AUGUST 1952

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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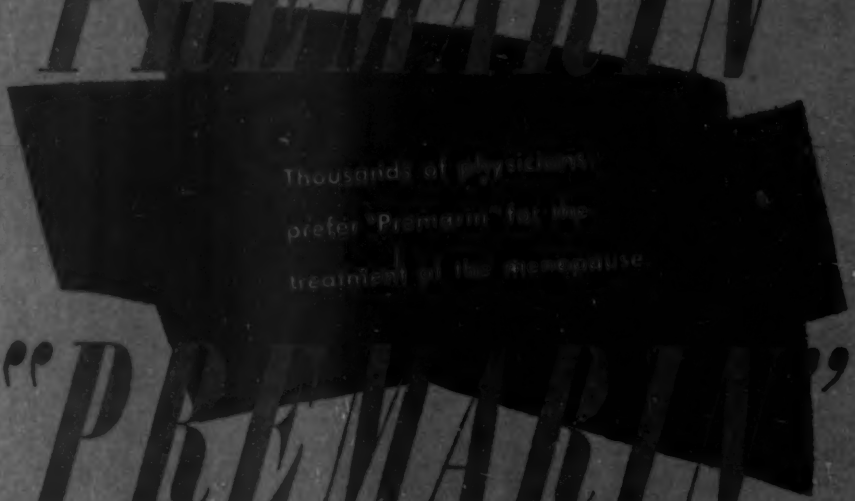

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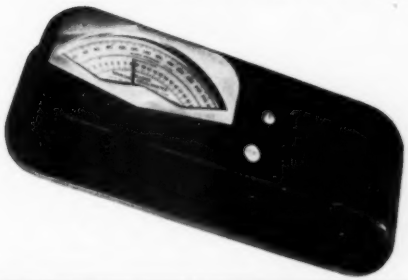

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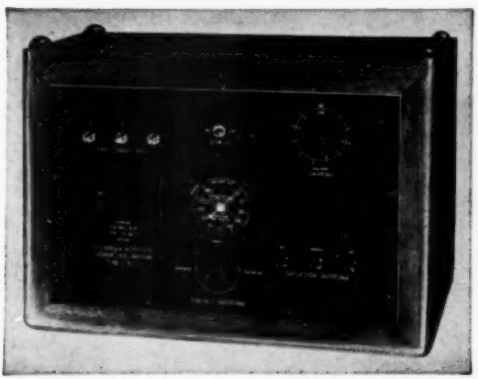

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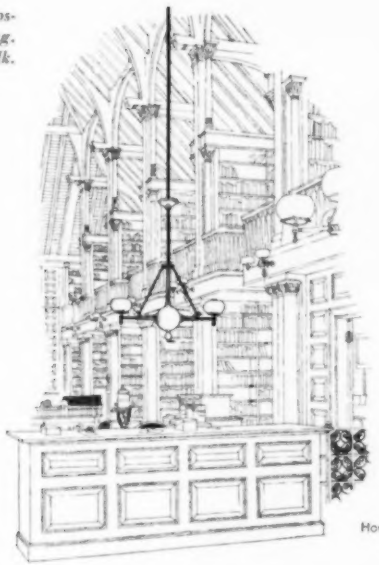

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 28, NO. 8 AUGUST 1952

A CRITICAL APPRAISAL OF CURRENT THERAPY IN RHEUMATOID ARTHRITIS*

With special reference to ACTH and Cortisone

CHARLES RAGAN, FELIX DEMARTINI, RONALD LAMONT-HAVERS
RALPH A. JESSAR, deGUISE VAILLANCOURT, ALBERT W. GROKOEST

I. INTRODUCTION

THE therapy of rheumatoid arthritis is complicated by several important factors. First, its pathogenesis is completely unknown, and for this reason an approach via an experimental animal is not possible. Secondly, its course is variable and modified by factors of which we have no knowledge and therefore have no control. Last year at the Graduate Fortnight[1] we presented evidence (which was open to criticism based upon the above points but which seemed to us to be valid) which showed that nothing we had done had modified the course of rheumatoid arthritis over a long period of follow-up.

We are reasonably certain that two approaches may modify the course beneficially, for short periods of time. The first is chrysotherapy

* Presented before the Section on Medicine at The New York Academy of Medicine, November 20, 1951.
From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York.
Supported in part by grants from the Masonic Foundation for Medical Research and Human Welfare, and the New York Chapter of the Arthritis and Rheumatism Foundation.
Cortisone supplied partly by Merck & Company, and partly from funds derived from the U.S.P.H.S., Research Grant No. A 21 (C). ACTH supplied by Armour and Company.

or gold therapy, the second is the conservative regimen of bed rest, supportive treatment, salicylates, antiphlogistic agents, and attempts to minimize deformities by orthopedic methods. But in our experience we have not been able to maintain a remission induced by gold in a significant number of patients. Patients who have achieved a remission on a sanitarium type of regimen have, when returned to their daily life, eventually relapsed. Probably, ideally, the latter regimen, that of the sanitarium, has a great deal in its favor, because of the length of the remission induced and also because of the lack of any great danger. Its strongest proponent is the group at the Massachusetts General Hospital, under Dr. Walter Bauer. In most places and in New York City, such a program is not feasible, chiefly for economic reasons because bed space is not available for a large number of patients. If any criteria were available for absolute prognosis, potentially severe disease could be treated this way, despite economic and social considerations, but such criteria are not available and it is questionable if one should resort to sanitarium type of care in a patient who will have a good prognosis without it.

Every year, since the older of us believed we had reached the age of medical reason and probably long before that, new therapies have been advocated for the treatment of rheumatoid arthritis. The list of suggested therapies has reached astronomical proportions and much of the time of the men interested in this field has been spent in refuting or confirming such allegations. Some workers have never been able to confirm any of them.

II. Terramycin

In recent years, we have done some clinical work on two suggested forms of therapy. The first is the use of terramycin in small doses as advocated by Brown.[2] In our experience little need be said concerning this form of therapy since, in the twenty-five patients we have treated in accordance with the regimen advocated by Brown, we have seen a significant remission in only one and a partial remission in two which is what we would expect with no therapy.

III. Hyperadrenalism Induced by Cortisone or ACTH

A. *Temporary Effect:* Although Dr. Hench and his group[3] have repeatedly stated that hyperadrenalism induced by cortisone or ACTH

in rheumatoid arthritis is not advocated as a therapy, it must at present receive consideration as such. This aspect cannot be dismissed with a paragraph and one might be considered overambitious to consider it even in this space. There is no doubt about the initial effect of induced hyperadrenalism in rheumatoid arthritis. In almost every patient—and the exceptions are so few as to be negligible—there is a marked improvement in the patient's general condition. I do not believe that fault will be found with this statement by anyone. What we wish to discuss is whether or not induced hyperadrenalism will modify the course of this chronic disease over a long period of time. One point should be made at the outset, that is, that some measure of hyperadrenalism seems to be necessary to produce a beneficial effect on the patient with rheumatoid arthritis and that when hyperadrenalism is terminated, the patient will resume the course of his disease uninfluenced by the temporary induction of hyperadrenalism. The increments of pain and activity of the disease which appear after the cessation of the hormones are extremely difficult to evaluate, but some people do feel that there may be an exacerbation of the disease following withdrawal of the hormones. This point remains unsolved and discussion of it with the data which are presently at hand seems fruitless. However, in a great many patients with rheumatoid arthritis, and particularly in those with severe chronic progressive disease, with whom we are concerned, the disease continues its course with few remissions. Therefore, one must face the prospect of sustained induced hyperadrenalism. This does *not* constitute physiological replacement therapy but represents the production of one pathological state in order to modify another pathological condition.

B. *Cushing's Syndrome—Spontaneous and Induced:* Recently, a review of Cushing's syndrome has appeared[4] and two tables taken from this paper are pertinent to this discussion. The first (Table I) shows the symptoms and signs seen in Cushing's syndrome and it is apparent that such have been seen in the hyperadrenalism induced by cortisone or ACTH. The notable exception is the presence of hypertension in most patients with naturally-occurring Cushing's syndrome while to date the presence of hypertension in induced hyperadrenalism has not been emphasized. However, in Figure 1, changes in the casual blood pressures of patients who have been on cortisone or ACTH for an average of nine months are charted and it can be seen that the trend is definitely towards one of hypertension. Table II is taken from the same

TABLE I—SYMPTOMS AND SIGNS IN PATIENTS WITH CUSHING'S SYNDROME*

Symptoms or Signs	*Columbia Series (33 cases)*	*Previously reported 189 cases*
Obesity	97%	97%
Hirsutism	73%	69%
Hypertension	84%	85%
Amenorrhea, Oligomenorrhea, Impotence in men	86%	71%
Purple striae	60%	71%
Mental symptoms (Major 24%, Minor 43%)	67%	31%
Weakness and backache	83%	50%
Poor wound healing or severe infection	42%	30%
Headache	58%	34%
Plethoric appearance	80%	50%
Purpura or easy bruisability	60%	23%
Acne, skin pigmentation or other rash	82%	26%
Ankle edema	60%	28%
Neurological symptoms or signs	39%	17%
Polydipsia or polyuria	39%	25%
Virilism	9%	5%
Exophthalmos	6%	8%

review[4] and shows the causes of death in Cushing's syndrome. In passing, it might be said the majority of these patients, unless some modification of their Cushing's syndrome occurred, were dead within five years of the onset of symptoms. There are notable exceptions to this, since a few of these patients have continued with full-blown Cushing's for more than five years.

C. "*Suboptimal*" *Dosage Schedules:* With this concept of the course of Cushing's syndrome in mind, and with the prospect of sustained induced hyperadrenalism in the treatment of rheumatoid arthritis facing us, one must of necessity restrict the degree of hyperadrenalism induced. This has been our policy from the beginning, and is the regimen described as the "suboptimal dose," whereby the patient's symptoms are not completely ameliorated but hyperadrenalism of only a minor degree is induced. The patients discussed have all been maintained on suboptimal levels of cortisone or ACTH whereby symptoms have persisted

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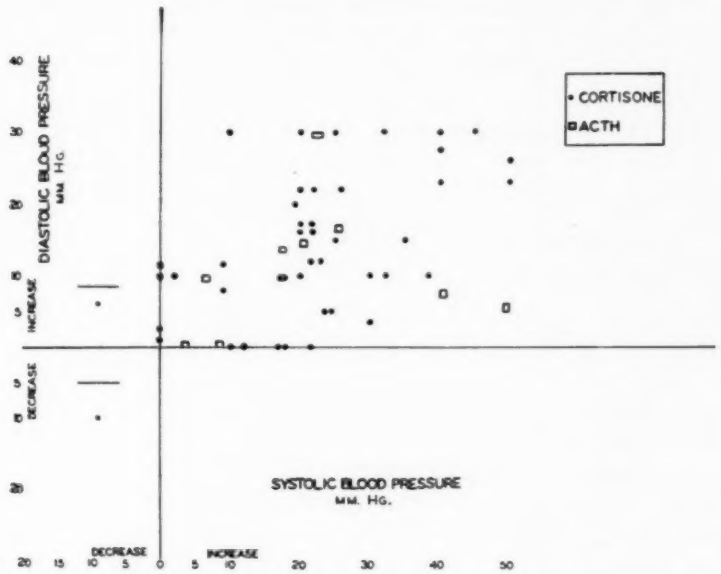

Fig. 1—Changes in casual blood pressures of patients with rheumatoid arthritis treated for a mean of 9 months with cortisone or ACTH.

TABLE II—CAUSES OF DEATH IN CUSHING'S SYNDROME (114 cases)
(multiple causes listed in 36 instances).

Infection	54 (6 tuberculosis, in 3 others tuberculosis present)
Cardiac failure	30
Cerebrovascular accidents	8
Uremia	6
Post-operative deaths	23 (8 in adrenal insufficiency)
Carcinoma of adrenal	6 (in 11 others, carcinoma present)
Tumor of thymus	6
Carcinoma of pancreas	4
Sympathicoblastoma	1
Acute gastrointestinal hemorrhage	2
Pulmonary infarction	4
Renal colic	1
Asthenia	2
Suicide	2
Not listed	4

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TABLE III—SUMMARY OF 59 PATIENTS WITH RHEUMATOID ARTHRITIS WHO HAVE BEEN TREATED WITH SUSTAINED INDUCED HYPERADRENALISM FOR PERIODS OF 3 TO 26 MONTHS A MEAN OF 9 MONTHS (As of 7/1/51)

Duration of disease	1 to 30 years
Sex	male 23, female 36
Age	13 to 78 years

Steinbrocker Classification:

Grade I— 0	Class I— 0
2—13	II—22
3—29	III—23
4—17	IV—14

Treatment:

Oral cortisone alone	5
ACTH alone	11
Intramuscular cortisone alone	31
daily	2
2 to 3 times a week	22
once a week	7
Various combinations of oral or intramuscular cortisone and ACTH	12

TABLE IV—CHANGE IN WORK CAPACITY DURING SUSTAINED HYPERADRENALISM (as of 7/1/51)

	Pretreatment	*During treatment*
Bedridden	10	4*
No work	21	3
Part-time work	24	21**
Full-time work	4	31
Using canes or crutches	33	12

Major flexion contractures persist in spite of exercises in addition to hormone in 5 patients.

Arthroplasty for correction of flexion contracture performed in 2 patients.†

New flexion contractures have developed, of minor degree, in 2 patients.

* 2 of these patients, for periods of 3 and 4 months, were on part- or full-time work but have again become bedridden.

** 2 of these patients died.

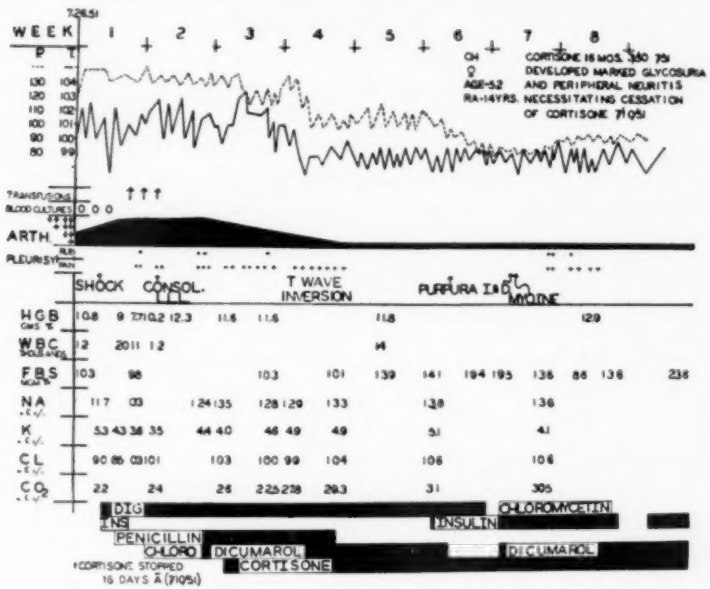
† these 2 patients are still bedridden after 12 and 9 months of hormone and 5 to 6 months after knee arthroplasty.

in minor degree in all instances. The degree of hyperadrenalism (i.e., the dosage of hormone) required to produce this effect is probably related to the severity of the disease. Thus, patients with severe disease require more hormone for an effect, and a greater degree of induced hyperadrenalism is needed. Patients with mild disease may be maintained on minimal amounts of hormone—e.g., under 75 mgm. daily by mouth—and the degree of hyperadrenalism will be minimal. A second factor in addition to the activity of the disease is the physical, mental and emotional activity of the patient. A patient on bed rest, at peace in the hospital may often be maintained on minimal dosages which become completely ineffective when he returns to his usual physical activity amid the turmoils of his home and work environment. We have attempted to assay the value of the hormones in the latter situation since our aim has been to evaluate their therapeutic effectiveness in contrast to sanitarium type care. We now have data on fifty-nine patients with rheumatoid arthritis of varying degrees (Table III), the majority of whom are severe as shown by the Steinbrocker classification.[5] These patients have been treated with induced hyperadrenalism for varying periods of time, from seven to thirty months, with an average of approximately ten to twelve months. There is no question but what we have achieved a better work record during induced hyperadrenalism than before the induction of the hormones (Table IV) and, by and large, some of these patients have passed through the year with no untoward effects at all.

D. *Hazards Noted during Treatment:* It is necessary to consider the troubles which appear during the induction of hyperadrenalism in the treatment of rheumatoid arthritis. These vary from minor ones such as injection abscesses to death. In Table V, we have outlined some of the complications which have been seen during the induction of hyperadrenalism. Figure 2 shows in detail the course of one patient who has subsequently died but who obviously presented a difficult therapeutic problem. The weight gain which occurs with these patients (Fig. 3) is difficult to control. This is not in general related to salt and water retention since in the patients shown in Fig. 3 the frequent use of mercurial diuretics did not result in a significant weight loss, and there is no evidence of peripheral edema. It has been stated[6] that the weight gain may be controlled by dieting but this has not been our experience. The appetite of some of these people verges upon the pathological, and

TABLE V—COMPLICATIONS ENCOUNTERED DURING SUSTAINED INDUCED HYPERADRENALISM (As of 7/1/51)

Age of Pt.	*Duration of hormone administration*	*Complications necessitating permanent cessation of hormone administration*
48	8 months	1. Thrombophlebitis with pulmonary infarction.
49	9 months	2. Bronchiectasis with overwhelming pulmonary infarction and death.
78	6 months	3. Dizziness, blurring of vision, mental confusion.
55	7 months	4. Pulmonary tuberculosis with positive sputum.
42	5 months	5. Suicidal attempt with barbiturates. (Manic-depressive psychosis necessitating shock therapy after short course of ACTH in the past.)
72	6 months	6. Cerebro-vascular accident and death.
73	9 months	7. Congestive failure, pneumonia, pulmonary infarction.
38	3 months	8. Patient felt improvement not worth the trouble.
56	4 months	9. Patient felt improvement not worth the trouble.
		Complications necessitating temporary cessation of hormone administration
51	16 months	1. Marked carbohydrate intolerance with furunculosis and peripheral neuritis.
63	10 months	2. Diverticular abscess with perforation and sinus tract formation requiring drainage and permanent colostomy. Pulmonary infarction in post-operative period.
55	17 months	3. Cerebro-vascular accident with recovery.
—	—	4. Pneumonia in 5 patients.
46	9 months	5. Acute cholecystitis and common duct obstruction requiring cholecystectomy and common duct exploration.
		Complications not requiring cessation of hormone administration
69	7 months	1. Carcinoma of parotid with facial palsy requiring biopsy and radiotherapy.
41	14 months	2. Appearance of new duodenal ulcer symptomatically controlled with reduction in salicylates and ambulatory ulcer regimen.
60	8 months	3. Appearance of new gastric ulcer still not well controlled symptomatically with salicylate withdrawal and ambulatory ulcer regimen.
53	2 months	4. Reactivation of old duodenal ulcer controlled by ambulatory ulcer regimen.
		5. Development of hypertension—diastolic over 90 in absence of pre-existing hypertension on ACTH—3; on cortisone—10.
		6. Hyperglycemia—fasting blood sugar above 120—7.
		7. Significant glycosuria—2 (1 a known diabetic before treatment). Both on cortisone.
		8. Acne—2. 1 on ACTH, 1 on cortisone.
		9. Inflammatory parotitis—1 on cortisone.
		10. Ecchymoses—5. 4 on cortisone, 1 on ACTH.
		11. Undue mental hyperreactivity—3. 1 on ACTH, 1 on cortisone, and 1 on both ACTH and cortisone.
		12. Hypokalemia (serum K below 3.4 mEq/)—3 on ACTH and 1 on cortisone.
		13. Amenorrhea—3. 2 on cortisone, 1 on ACTH.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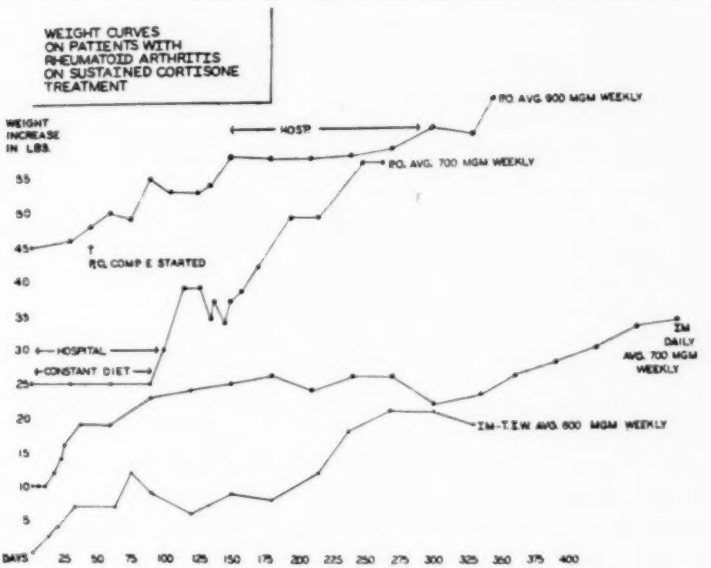
CORTISONE STOPPED
16 DAYS

Fig. 2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RHEUMATOID ARTHRITIS
ON SUSTAINED CORTISONE
TREATMENT
WEIGHT
INCREASE
IN LBS.
HOSP
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DAYS

Fig. 3

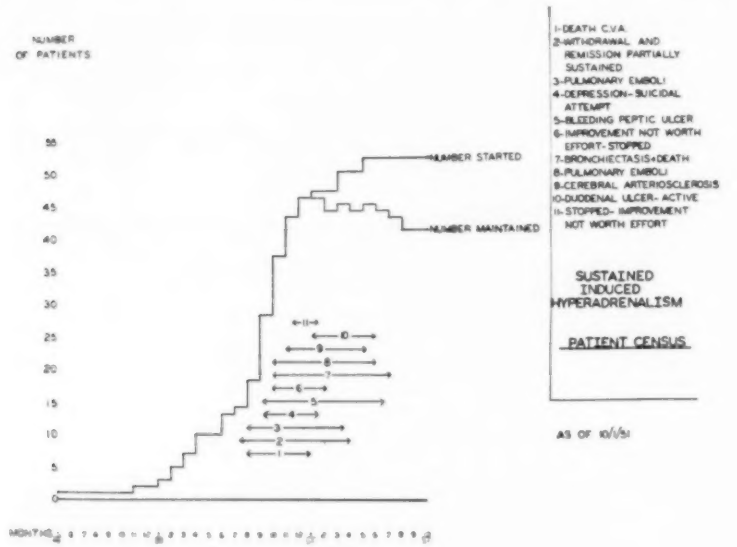

Fig. 4

we have not been able to modify the weight gain in some of them by restriction of caloric intake on an ambulatory, out-patient basis.

E. *Summary of "Suboptimal," Ambulatory Treatment:* At this time, it is very difficult for us to state whether induced hyperadrenalism at suboptimal levels will modify the course of the disease. In certain individuals there is no question but that we have achieved this over a period of a year or more without any untoward effects. On an overall basis, the outlook is not too encouraging, since in many instances the patients who are doing extremely well are the patients with mild disease who might have done well without induced hyperadrenalism. It will take at least two or three additional years before we can say whether or not we have modified the course of the disease. One discouraging point is that the number of patients who can be controlled indefinitely is apparently decreasing as time goes on (Fig. 4). It should be stressed that we have not been timid in maintaining hyperadrenalism and have terminated it only when we have felt that it was absolutely necessary, since the withdrawal of these hormones is a difficult period for both patient and physician.

F. *Combination of Sanitarium Care and Cortisone:* We have another small group of patients with severe disease who are being cared for in a sanitarium atmosphere.* The criterion used to admit patients to this study has been that they had been confined to a bed or wheelchair for a year. We are attempting by the use of simple physical measures such as active and passive exercises against resistance, salicylates and cortisone to attempt to rehabilitate these patients. Although these patients are undergoing sanitarium therapy, the severity of their disease has been so great that we have not been able to keep the dosage to the so-called safe levels and the average dose required has been 100 mgm. daily intramuscularly. Weight gain has been a problem and one psychosis has been seen. There have been no other troublesome effects of hyperadrenalism. To date, this group has been disappointing and the effect of cortisone may be described as solely antiphlogistic. We have not achieved an increase in range in motion or an increase in muscle strength. Although it is perhaps far too early to expect dramatic improvement since these patients have received hormone for an average of only nine months, the outlook is not too encouraging.

Last year at the time of the Graduate Fortnight,[1] hope was held out that the 10 to 15 per cent of patients with rheumatoid arthritis who were confined to bed at home or in institutions[7] might be rehabilitated by the use of cortisone with all other adjuncts of therapy. This hope is now somewhat dimmer. We have attempted in a few patients to use cortisone in conjunction with orthopedic surgical procedures to correct severe deformities.** For some, it has been possible to increase joint mobilization, for others it has been a complete failure.

G. *Wound-healing at "Suboptimal" Dosage Levels:* A brief word about wound healing might be pertinent here. It can be said that, at the usual doses of cortisone administered to humans, incised skin wounds are of no great concern when sutured if the sutures are left in situ for an additional three to four days. Such wounds have healed adequately, to the best of our knowledge. Open granulating wounds will fill in slowly but ultimately will heal. We have been concerned with another type of wound-healing—namely, that following an intestinal anastomosis —and when a gastro-enterostomy has been necessary, we have felt it

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** In conjunction with Drs. Frank Stinchfield and Charles Ryder of the New York Orthopedic Hospital. Detailed reports will be published at a later date.

necessary to stop cortisone or ACTH. It should be emphasized that in a critical situation, sudden withdrawal of cortisone with at least temporary adrenal atrophy is fraught with danger. Under such circumstances, 25 mgm. of ACTH intravenously in a slow infusion given daily for two or three days concurrently with cortisone has, in most instances, sufficed to prevent adrenal atrophy when both hormones are withdrawn at the same time.

H. *Cortisone vs. ACTH:* Some mention should be made concerning the therapeutic effectiveness of cortisone versus ACTH. Patients receiving ACTH have done equally as well as patients receiving injectable and oral cortisone. There is no question but what oral cortisone is the least troublesome. Injection abscesses have occurred with both ACTH and cortisone given parenterally. These are inclined to spread widely when the patient is in the hyperadrenal state and it has been our practice to discontinue the hormone when an abscess develops. The time required for localization of abscesses has been prolonged and all have required surgical drainage. Long-acting preparations of ACTH in gelatin have recently appeared. We have had only brief experience with such preparations but have found them to be effective for periods of 24 to 36 hours. We are not certain whether our patients prefer it to aqueous ACTH given every 8 to 12 hours. It is slightly more irritating but not sufficiently so to make much difference. For technical reasons, it is much more difficult for the patient to handle at home by himself than aqueous ACTH. Oral cortisone is much simpler to use but its effect is more transitory than injectable cortisone. We have not been able to maintain two of our patients with severe disease satisfactorily with large doses of oral cortisone but have been able to do so with reasonable amounts of injectable hormones.

Summary

The greatest usefulness of induced hyperadrenalism in rheumatoid arthritis apparently lies in the treatment of the early case with a poor prognosis. As mentioned above, when discussing sanitarium type of care, it is impossible to predict with any degree of certainty which patient with rheumatoid arthritis will end badly. In a few patients early in the disease we have felt reasonably assured that the prognosis was grave. This assurance was based on the rapid progression of the disease in the early months, an early appearance of deformities, a failure to re-

spond to salicylates when combined with bed rest over a short period of time and on the presence of a positive agglutination against hemolytic streptococci and a positive sensitized sheep cell agglutination early in the disease. In these few patients, hyperadrenalism has been induced early and sustained and we have the impression that we have achieved a major therapeutic triumph by decreasing the tempo of the disease. These patients are developing minor deformities and minor destructive lesions by x-ray even while hyperadrenalism has been sustained. However, the tempo of their disease is such that they have been able to pursue their daily activities rather than be confined to a bed or chair existence, an event which we believe might have taken place had we not started induced hyperadrenalism early. Thus, the therapy of rheumatoid arthritis with induced hyperadrenalism appears to have advantages similar to the other types of therapy advocated for this disease, since in all advocated therapies the early cases do better than the late cases. The mild cases which are said to be kept in remission with small doses of hormone by mouth with little or none of the troubles of hyperadrenalism cannot be fairly assessed since under any form of therapy such patients tend to do well. In those who are unfortunate enough to have had the disease in such severity that they have been confined to a bed or chair existence and have become invalids, the prognosis for a return to a useful existence when cortisone or ACTH is added to the therapeutic armamentarium is in our hands not much better than without it. The effect of these hormones on such patients is an antiphlogistic one whereby the patient is made more comfortable but is not restored to a full life. Time will tell whether in such patients the hazards of therapy will, in the long run, not outweigh such palliation. In the early cases with a potential leading to an invalid existence, we now feel the hazards should be faced as a calculated risk to prevent or diminish the invalidism which may be anticipated.

The crying need in the present treatment of rheumatoid arthritis is for an understanding of the pathogenesis of the disease particularly its etiological factors, and for some definitive indices of a poor prognosis early in the disease. With the latter available, the tools are at hand to prevent invalidism, at least for some years. These tools all have dangers or disadvantages but with assurance that a reasonably certain invalidism might be avoided, the dangers and disadvantages could be faced much more squarely than is possible in our present state of indecision.

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THE CONSERVATIVE MANAGEMENT OF ACUTE URINARY SUPPRESSION*

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In the past few years patients with acute urinary suppression have been treated by a variety of different procedures. One approach has been directed at the alleviation of nitrogen retention and the correction of derangements in electrolyte patterns of the blood. The methods employed have included the artificial kidney, peritoneal dialysis, intestinal irrigation, and exsanguinotransfusion. At first the results obtained by these means did not differ significantly from the natural history of acute urinary suppression treated by random medical management alone.[1] More recently, dialyzing techniques have been improved, particularly in the instance of the artificial kidney, so that a continual appraisal of their therapeutic efficacy must be made. At the same time, the outlook for the anuric patient managed conservatively without dialyzing procedures has improved greatly as a result of more thorough familiarity with the physiology of fluid balance, electrolyte relationships, and protein metabolism. In the interest of providing a control series it seems timely to review current concepts of conservative treatment and to state the results obtained.

I should like to discuss in detail the major physiological and biochemical disturbances that occur during acute urinary suppression, to reiterate the causes of death in fatal instances, to review the extent to which the syndrome can be modified by conservative measures, and to set forth the outcome of conservative treatment alone in thirty-seven consecutive instances of severe urinary suppression seen at the Columbia Presbyterian Medical Center. In each of these thirty-seven patients the urinary output was less than 100 cc. a day for three or more consecutive days.

Natural History: The various causes of acute urinary suppression

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TABLE I—THE RELATIONSHIP OF THE MAXIMUM DEGREE OF NITROGEN RETENTION AND ELECTROLYTE ABNORMALITY TO THE DURATION OF URINARY SUPPRESSION IN TWENTY-TWO SURVIVING PATIENTS*

			Serum concentrations					
Name	*Age*	*Cause of urinary suppression*	*NPN mg.%*	*BUN mg.%*	*K mEq/L*	*Na mEq/L*	*CO_2 mEq/L*	*Duration of Suppression*
I.W.	18	Diabetic acidosis with shock		122	7.1	—	6.9	15 days
E.S.	32	Mercury bichloride poisoning		206	—	—	17.5	14 days
H.B.	29	Transfusion reaction		225	—	—	—	13 days
H.Q.	36	Carbon tetrachloride poisoning	192		—	—	—	12 days
L.H.	39	Transfusion reaction		113	—	—	22.2	12 days
G.G.	31	Postpartum suppression	139		—	—	—	12 days
M. T.	38	Pentachlornaphthalene poisoning		142	—	—	21.2	10 days
H.B.	33	Bacitracin toxicity		127	3.8	135	17.3	10 days
E.L.	34	Transfusion reaction	129		—	—	19.4	8 days
F.H.	63	Diabetic acidosis with shock		150	6.0	122	4.2	7 days
R.W.	37	Carbon tetrachloride poisoning	94		—	—	—	6 days
E.R.**	40	Carbon tetrachloride poisoning		210	6.0	132	17.3	14 days
E.S.**	60	Transfusion reaction		181	6.5	144	14.0	14 days
M.H.	31	Ulcerative colitis with shock		280	4.4	125	15.9	14 days
R.R.	24	Carbon tetrachloride poisoning		212	6.7	116	14.5	12 days
M.G.	37	Induced abortion		226	10.3	129	7.4	12 days
L.S.**	32	Postpartum hemorrhage with shock		217	7.5	119	13.2	10 days
J.C.	28	Carbon tetrachloride poisoning		188	5.9	125	17.3	9 days
M.V.	56	Transfusion reaction		162	8.0	134	38.2	9 days
C.W.	21	Carbon tetrachloride poisoning		114	—	122	23.0	8 days
G.F.	37	Carbon tetrachloride poisoning	228		6.0	120	14.5	7 days
V.R.	24	Postpartum suppression	159		9.5	116	14.5	7 days

* The last eleven patients were managed subsequent to 1947.
** Treated with a cation exchange resin.

(among which shock, intravascular hemolysis, obstetrical diseases, and renal poisons are the chief agents) produce but one clinical picture as far as the renal lesion and its sequellae are concerned. This syndrome includes varying degrees of suppression of urine formation, sometimes progressing to complete and absolute anuria for eighteen days. All the clinical and laboratory manifestations of severe uremia ensue. Convulsions, periorbital edema, uremic pericarditis, and marked hypertension with cardiac failure, hypertensive encephalopathy, and hypertensive retinopathy can occur. More than one instance of marked thrombocytopenic purpura has been noted, particularly in association with the pathological picture of bilateral renal cortical necrosis.

Of greatest importance is the fact that urinary suppression, when due to the causes enumerated, is self-limited in duration and spontaneously reversible in all of its clinical manifestations. Hypertension regularly subsides, and follow-up studies have disclosed normal renal function as measured by the usual simple clinical tests in all patients but one. This patient had had presumed bilateral renal cortical necrosis in another hospital, recovered from the acute episode, but subsequently developed calcification of both renal cortices and died of irreversible renal insufficiency several years later. It is apparent from the observations in Tables I and II that diuresis and recovery spontaneously occur at some time prior to nineteen days, provided the patient can be tided over the critical anuric phase of his disease. The basis of our present concept of treatment rests upon this finding.

Conservative Management

Initial Program: Initially the physician carries out specific measures designed to ameliorate renal damage. These include the correction of shock, the prompt alkalinization of blood in instances of intravascular hemolysis, and the immediate administration of British anti-Lewisite to patients with mercury poisoning, provided this can be done two or three hours after ingestion.[2] Once this initial phase has passed, suppression of urine formation follows.

Three distinct approaches have been advocated for subsequent management, either singly or in combination. *A.*) Procedures have been described which aim at producing an artificial diuresis. These include diuretics, bilateral renal decapsulation, and various denervation techniques, such as: surgical stripping of the renal vessels, spinal anesthesia,

TABLE II

THE RELATIONSHIP OF THE MAXIMUM DEGREE OF NITROGEN RETENTION AND ELECTROLYTE ABNORMALITY TO THE DURATION OF URINARY SUPPRESSION AND THE CAUSE OF DEATH IN FIFTEEN FATALITIES*

Name	*Age*	*Cause of suppression*	*Cause of death*	*Serum concentrations*					*Duration of suppression*	*Autopsy*
				NPN mg.%	*BUN mg.%*	*K mEq/L*	*Na mEq/L*	*CO2 mEq/L*		
G.M.	31	Ureteropelvic obstruction	Uremia	227		5.7		25.4	50 days	Ureteropelvic obstruction due to bilaterally aberrant renal arteries and veins
W.L.	55	Transfusion reaction	Pulmonary edema		150			16.0	12 days	Pulmonary edema "hemoglobin nephrosis"
H.S.	51	Transfusion reaction	Generalized peritonitis following pancreatectomy	132					10 days	Generalized peritonitis "hemoglobin nephrosis"
C.H.	79	Transfusion reaction	Sudden and unexplained. EKG not taken		120	7.0	127	21.1	8 days	"Hemoglobin nephrosis" acute right pyelonephritis and acute cholecystitis
M.J.	63	Sulfadiazine nephrosis	Pulmonary emboli		96			34.6	8 days	Multiple pulmonary emboli and infarctions. Sulfadiazine nephrosis
A.G.	62	Intravascular hemolysis due to sulfanilamide	Anemia, congestive failure and uremia	380				12.2	8 days	"Hemoglobin nephrosis" Congestive heart failure
E.R.	53	Acute glomerulonephritis	Sudden and unexplained. EKG not taken		145				7 days	Acute glomerulonephritis, right. Absent left kidney
A.S.	24	Postpartum suppression	Sudden and unexplained. EKG not taken	136					7 days	"Lower nephron nephrosis"

TABLE II—(*Continued*)

Name	*Age*	*Cause of suppression*	*Cause of death*	*Serum concentrations* NPN mg.%	BUN	K mEq/L	Na mEq/L	CO_2 mEq/L	*Duration of suppression*	*Autopsy*
C.F.	86	Sulfathiazole nephrosis	Pneumonia, cardiac failure, and uremia	190					7 days	Sulfathiazole crystals in tubules, ureter, and bladder; bronchopneumonia; arteriosclerotic heart disease with congestive heart failure
M.T.	32	Postpartum suppression	Pulmonary edema	80				13.2	7 days	None
R.B.	57	Shock, peritonitis, ileus	Generalized peritonitis after abdominal operation	104					6 days	None
E.L.	28	Postpartum suppression	Cerebral hemorrhage occurring one week after diuresis; Thrombocytopenic Purpura		290	7.2	120	9.2	19 days	Cerebral hemorrhage Bilateral cortical necrosis with beginning regeneration of renal tubules
G.T.	39	Carbon tetrachloride poisoning	Acute yellow atrophy of the liver; residual uremia		201	8.0**	128	19.7	16 days	Acute yellow atrophy of the liver and renal tubular necrosis with beginning regeneration
A.P.	66	Chronic and acute pyelonephritis; solitary kidney	Arteriosclerotic heart disease with pulmonary edema; uremia		155	6.9	126	10.0	5 days	None
N.B.	28	Not known; followed incision and drainage of broad ligament abscess	Potassium intoxication		70	8.6	113	20.0	5 days	Normal organs, including kidneys.

* The last four patients were managed subsequent to 1947.
** Serum potassium concentration decreased after administration of cation exchange resins.

caudal block, and the injection of drugs whose action blocks the autonomic nervous system. These methods have not met with consistent success. *B.*) There are conservative measures available to every physician directed at maintaining normal fluid balance and keeping the retention of solutes to a minimum by dietary control and the regulation of electrolyte balances. *C.*) Dialyzing methods have been designed to create an extrarenal pathway for the excretion of solutes and, in this way, to alleviate azotemia and electrolyte disturbances. I shall consider only the conservative approach.

Fluid Balance: The figure usually given for insensible fluid loss is in the neighborhood of one liter. In the presence of urinary suppression the body has no satisfactory mechanism for removing fluid administered in excess of this amount. In years past much harm has been done by the administration of large quantities of parenteral and oral liquid, resulting in increased blood volume, cardiac embarrassment, peripheral edema, intractable pulmonary edema, and death. The greatest number of fatalities in urinary suppression in past years have not been due to uremia or potassium intoxication, but pulmonary edema.[1] Excepting the factor of increased pulmonary capillary permeability resulting directly from the uremic state itself, this severe form of circulatory failure can be prevented by replacing only that amount of fluid lost by the body and no more. This implies an estimation of insensible water loss, careful measurement of any urine, all vomitus, diarrheal stools, loss by saliva (which in the instance of mercurial stomatitis may amount to more than one liter a day), and replenishing the total daily fluid deficit, volume for volume. In the past it has been repeatedly observed that pulmonary edema results from the administration of as little as two to three liters of fluid a day.

Protein Metabolism: The second cornerstone of conservative therapy concerns itself with attempts to keep nitrogen, potassium, and other solute retention to a minimum. Because a fasting man rapidly exhausts carbohydrate stores and must, therefore, supply his caloric needs by burning approximately 80 Gm. of tissue protein and 200 Gm. of body fat daily, ketosis sets in, and large quantities of protein degradation products, including potassium, are liberated into the extracellular water. If, on the other hand, this hypothetical starving man consumes carbohydrate, glucose will be burned in preference to fat, and ketosis will not occur. In addition, protein degradation and the consequent accumulation of nitrogenous wastes and potassium will be appreciably reduced. This

anti-ketogenic and protein sparing action of carbohydrate has been described in considerable detail by Gamble.[3]

In a starving man ketosis can be completely prevented by the administration of 100 Gm. of carbohydrate. For our purposes, however, it is also necessary to determine to what extent tissue protein degradation can be reduced by carbohydrate and to ascertain how much carbohydrate must be administered to achieve this maximum protein sparing action. In this connection Bull[4] in England and Borst[5] in Holland have advocated a 2,500 calorie diet, largely in the form of tremendous quantities of sugar, butter, and peanut oil. However, no single experimental study is available to substantiate the claim that this order of magnitude of caloric consumption is necessary to spare maximum amounts of protein. In fact, when the effect of increasing increments of carbohydrate intake, ranging from 50 to 1,000 Gm., is examined, it is apparent that the protein sparing action of carbohydrate reaches a limit at about 100 Gm. in normal man. The administration of additional carbohydrate does not spare additional protein. This conclusion can be verified by combining the individual data of Gamble,[3] Bull,[4] Borst,[5] Smith,[6] Johnson,[7] and Benedict,[8] and converting their figures into comparable terms of expression.

This saving, in terms of Strauss' calculations,[9] means that the patient who would ordinarily metabolize 70 Gm. of tissue protein per day if starved will actually degrade only 37.5 Gm. of protein if given 100 Gm. of carbohydrate daily. To put it another way, the administration of glucose to the anuric patient cuts the theoretical rate of non-protein nitrogen retention from 22 mg. per cent per day to 12 mg. per cent per day. These observations represent an unusual physiological bargain, even granting that in any one clinical instance, fever, infection, and hemolysis will increase protein catabolism. To what extent this additional renal solute load can be modified, if at all, by a carbohydrate intake increased above 100 Gm. is at the present time not known.

In regard to sources of food energy other than carbohydrate, under subcaloric conditions ingested protein is oxidized in support of energy metabolism and merely adds to the renal solute load.[3] Therefore, dietary protein is specifically contraindicated in the conservative management of acute urinary suppression. Fat serves no useful purpose except as a source of calories. Because of the difficulties of administering fat to sick patients, it has not been included in many medical regimens.

In actual clinical practice it is somewhat difficult to illustrate under controlled conditions the protein sparing action of carbohydrate. The experiments of Leifer and his associates[10] have demonstrated in the mouse that urea is degraded within the body and partially excreted through the lungs as carbon dioxide. For this reason the rate of retention of serum urea nitrogen in anuria cannot be considered an accurate index of protein breakdown, but merely an approximation. Nevertheless, review of data in anuric patients discloses in general lower serum urea nitrogen and non-protein nitrogen concentrations in those patients who were given an adequate carbohydrate ration. In this connection, patient G.M. (Table II), was given more than 100 Gm. carbohydrate daily. Over the fifty days that she experienced urinary suppression the non-protein nitrogen (N.P.N.) concentration of the serum rose to only 227 mg. per cent, an average rate of increase of 4.5 mg. per cent per day. Patient I.W. (Table I) was treated similarly over a fourteen day period of suppression. Her serum urea nitrogen (B.U.N.) concentration rose to a maximum of 122 mg. per cent, an average rate of increase of less than 8 mg. per cent per day. On the other hand, patient E.S. (Table I) was not given adequate carbohydrate, and during a fourteen day period of suppression the serum urea nitrogen (B.U.N.) concentration rose to 206 mg. per cent, an average rate of increase of 14 mg. per cent per day. These three examples were chosen because they occurred in patients who did not exhibit fever, infection, hemolysis, or other clinical complications apt to modify the basic rate of protein catabolism. They therefore represent as controlled an experiment as was possible and indicate in a practical manner the advantages of carbohydrate feeding.

Electrolyte Balance: In addition to close attention to fluid balance and the absolute insistence on a daily ration of at least 100 Gm. of glucose, management also concerns itself with electrolyte balance and acid-base relationships. For every gram of tissue protein degraded slightly more than 2 mEq. of potassium are liberated into the extracellular water, so that the protein sparing action of carbohydrate also serves to reduce the accumulation of this cation as well as sulfates and phosphates. Inevitably, however, some protein is degraded, resulting in increases in the serum potassium concentration. In most patients in whom protein catabolism can be depressed by carbohydrate this will not prove a serious feature, provided that no potassium is administered either in the form of food or parenteral solutions. It is also probable that under

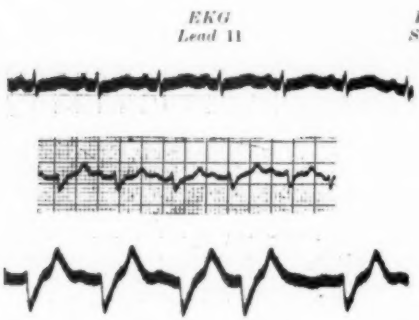
certain circumstances potassium is lost to the extracellular fluid in considerable amounts without actual cell destruction.

With the advent of cation exchange resins a very effective and eminently practical method became available for the treatment of potassium intoxication and the maintenance of normal serum potassium levels despite prolonged periods of urinary suppression. At the Columbia Presbyterian Medical Center the ammonium or sodium salt of a carboxylic acid resin ("Carbo-resin," Eli Lilly and Company, Indianapolis) has been employed. It is generally agreed that the oral route is more effective, although the resin can be administered rectally to advantage when necessary. Rectally a yield of ⅓ mEq. of potassium per gram of resin can be anticipated if the enema is retained. Elkington and his associates[11] have succeeded in removing up to 70 mEq. of potassium per day by the rectal administration of a resin. By varying the relative proportions of ammonium and sodium in a carboxylic acid resin very accurate control can be maintained over both the serum sodium and the serum potassium concentration. As illustrated in Fig. 3, hyponatremia may be corrected.

Patient G.T. (Fig. 3) exemplifies the very satisfactory manner in which the oral administration of 45 Gm. of the sodium salt of a carboxylic acid resin daily will simultaneously correct a preexisting hyperkalemia and hyponatremia in the face of continuing severe urinary suppression. Care must be exercised not to create hypernatremia by the excessive administration of the sodium salt of a resin. In this connection, cognizance must be taken of the fact that the resin will continue to act in the intestine for several days after oral administration has been discontinued.

If a more immediate decrease in the serum potassium concentration is desired than can be accomplished by cation exchange resins, advantage has been taken of the fact that the deposition of glycogen in the liver and muscles is accompanied by the storage of potassium. This results in a shift of potassium from the extracellular to the intracellular phase, with consequent reduction of the serum potassium concentration and temporary alleviation of the hazards of potassium toxicity. Such a shift can be accomplished by the simultaneous administration of glucose and insulin, although the reaction is reversible in a few hours. For this reason the procedure must be repeated frequently until a cation exchange resin has begun to exert an appreciable effect. Patient M.G.

Patient N.B.



EKG Lead II	Days of Suppression	Serum Concentration K mEq/L	Na mEq/L	CO_2 mEq/L	BUN mg%
	3	8.0	113	23	44
	4	8.0	114	22	51
	5	8.6	113	20	70

Fig. 1—Development of fatal potassium intoxication without appreciable change in serum electrolytes

This woman developed urinary suppression of unknown cause following uterine dilatation and curettage with incision and drainage of a resultant broad ligament abscess at another hospital. Marked hyponatremia, hyperkalemia, and acidosis were early complications of her disease. Potassium toxicity ensued, ending fatally in a ventricular arrhythmia, in spite of the fact that the serum electrolyte concentrations did not appreciably change and that the patient was given moderate quantities of glucose and insulin. Cation exchange resins were not administered.

(Fig. 2) demonstrates a lowering of the serum potassium concentration and reversibility of electrocardiographic abnormalities with the administration of glucose and insulin despite persistent anuria. These measures have not always been effective, however, when used alone (Fig. 1) and should, therefore, be considered as only an adjuvant to resin therapy.

There are several unusual and poorly understood aspects of potassium intoxication that warrant illustration. Figures 1, 2, and 3 depict three instances of hyperkalemia in which the absolute level of the serum potassium concentration bore little or no relation to the development of cardiac toxicity as measured clinically by the electrocardiogram. Patient N.B. (Fig. 1) was found initially to have hyperkalemia and marked hyponatremia with a normal electrocardiogram. She gradually developed the electrocardiographic signs of potassium intoxication, which ended fatally in a ventricular arrhythmia two days later, despite the fact that throughout the entire period of observation her serum potassium, sodium, and carbon dioxide concentrations did not appreciably change. On the other hand, patient M.G. (Fig. 2) illustrates a rather linear relationship between serum potassium concentration and

Patient M.G.

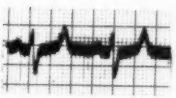
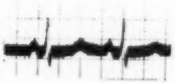
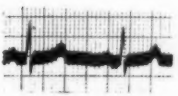
EKG Lead II	*Days of Suppression*	*Serum Values* K *mEq/L*	Na *mEq/L*	CO_2 *mEq/L*	*BUN mg%*
	10	10.4	129	7.4	226
	11	8.7	130	9.4	217
	11	7.3	129	9.4	217
	14	6.0	136	13.7	168

Fig. 2—Potassium intoxication corrected by glucose and insulin

Urinary suppression in this woman developed following an induced abortion. She did not seek hospitalization until the tenth day of suppression, at which time there was marked hyperkalemia, acidosis, and moderate electrocardiographic signs of potassium intoxication. She was given large and repeated injections of glucose and insulin on days ten and eleven, with reversal of electrocardiographic abnormalities and a fall in the serum potassium concentration. The urinary output began to increase on day twelve. Cation exchange resins were not administered.

cardiac toxicity as measured by the electrocardiogram. Patient G.T. (Fig. 3), with comparable elevations of the serum potassium concentration, exhibited no electrocardiographic abnormalities. Obviously, so-called "potassium intoxication" depends upon many factors besides the absolute serum concentration of potassium. That hyponatremia and acidosis aggravate the toxic effects of hyperkalemia has been proposed by Merrill[12] and borne out by his observations. Clinically it would appear that both electrolyte (sodium, potassium, and carbon dioxide) and electrocardiographic studies must be carried out before the dangers of potassium intoxication can be appraised. In addition, correction of coexisting hyponatremia and acidosis is indicated, since these factors apparently potentiate the toxic effect of hyperkalemia.

Patient G.T.

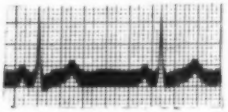
EKG Lead II	Days of Suppression	Serum Values K mEq/L	Na mEq/L	CO_2 mEq/L	BUN mg %
	6	6.4	132	21.4	149
	8	8.0	128	19.7	181
	9	6.2	135		
	10	6.2	138	23.0	201
	11	5.6	138	22.2	
	13	5.3	142	25.6	195
	14	4.5	147	27.4	

Fig. 3—Hyperkalemia and hyponatremia corrected by a cation exchange resin

In this man carbon tetrachloride poisoning produced urinary suppression with moderate hyperkalemia, slight hyponatremia, and slight acidosis, but no electrocardiographic abnormalities. 45 Gm. of the sodium salt of a carboxylic acid resin was given orally daily from day eight to day fourteen, with the correction of hyperkalemia, hyponatremia, and acidosis in spite of continuing marked urinary suppression. The patient did not increase his daily urinary output above 100 cc. until day fifteen. Glucose and insulin were not employed.

As phosphates, sulfates, and other acid metabolites accumulate in direct proportion to the amount of tissue protein catabolized, there is a natural tendency for patients with urinary suppression to develop acidosis. This can be partially prevented by the ingestion of an adequate carbohydrate ration and corrected in part by the periodic administration of small quantities of alkali.

In summary, the conservative management of acute urinary suppression consists of the administration of one liter of fluid daily plus the volume of measurable fluid loss, the daily ration of at least 100 Gm. of carbohydrate, the periodic administration of small quantities of alkali, and the use of cation exchange resins and glucose and insulin where indicated to avert potassium toxicity. During the recovery phase, when diuresis begins, urine is excreted before the maximum reabsorptive function of the renal tubules has been restored. As a result, large quantities of water and electrolytes, having the approximate composition of a glomerular filtrate, are lost. While serious electrolyte depletion and

dehydration are infrequent sequelae, the possibility of such a complication can be easily averted by simple replacement therapy.

Results of Conservative Management: Any appraisal of the results of treatment of acute urinary suppression must take into account the extreme variability of the disability with respect to both severity and duration of the loss of renal excretory function. Many patients exhibit only a transitory and mild oliguria that usually escapes the notice of the physician. Others develop virtually complete anuria for periods as long as sixteen days. In order to minimize this variable, only adult patients who had a measured urinary output of less than 100 cc. a day on three or more consecutive days were included in this study. With these criteria it was consistently found that urinary suppression persisted for considerably longer than three days. In fact, the duration of suppression in these patients, until the first day they were able to form one liter of urine, ranged from six to fifty days, with an average duration of eleven days. These criteria were selected to represent the most severe form of urinary suppression encountered clinically and to evaluate the results of conservative management in the most critical light possible for comparison with other procedures.

A second variable enters into consideration of the results of therapy in urinary suppression. This concerns itself with the severity of diseases that coexist with the renal lesion. Table II illustrates that physiological disturbances in other systems of the body, that developed independently of urinary suppression, are responsible for the majority of fatalities. Variabilities of this nature are impossible to control, but presumably will be present to the same degree in all consecutive series of patients chosen from an heterogeneous hospital population.

Since 1930 thirty-seven patients fulfilling these criteria have been encountered. Twenty-two patients recovered, a survival rate of 59 per cent. Two patients in this series did not have a reversible renal lesion and properly should not be included in a consideration of the treatment of self-limited urinary suppression. One of these (G.M., Table II) had mechanical obstruction of both ureters at the uretero-pelvic junction. The second (A.P., Table II) had chronic pyelonephritis involving a solitary kidney, with urinary suppression presumably resulting from superimposed acute infection, although permission for autopsy was not granted. The corrected survival rate for reversible forms of urinary suppression encountered since 1930 is, therefore, 63 per cent.

Prior to 1947 patients in this series were treated by random medical management, occasionally overloaded with fluids, and not supplied with an adequate carbohydrate ration. Conservative measures for treating potassium intoxication had not been realized. The overall survival rate for the twenty-two patients in this earlier group was 50 per cent.

Since 1947 fluid balance has been cautiously controlled. An adequate carbohydrate intake has been insisted upon. Glucose and insulin have been employed in all instances of potassium intoxication, and more recently cation exchange resins have also played a part in therapy. Of the fifteen patients in this more recent group, four died, and eleven recovered—an overall survival rate of 73 per cent. This can be corrected to 80 per cent if only reversible forms of urinary suppression are considered.

Among the three fatalities in patients with reversible urinary suppression treated since 1947, one death (E.L., Table II) resulted from cerebral hemorrhage seven days after the onset of diuresis at a time when all manifestations of uremia were subsiding and the serum urea nitrogen (B.U.N.) concentration had decreased 72 mg. per cent. A second death (G.T., Table II) similarly occurred during the recovery phase of the disease. At autopsy this fatality was thought to have been the result of acute yellow atrophy of the liver secondary to carbon tetrachloride poisoning, although residual solute retention might have played a contributory role. The third fatality was caused directly by potassium intoxication (N.B., Table II), and probably could have been prevented if cation exchange resins had been employed.

These results in fourteen patients with reversible urinary suppression treated since 1947 indicate a survival rate of 80 per cent. Muirhead, Vanatta, and Grollman,[13] using slightly less rigid criteria of patient selection, reported twenty-seven consecutive instances of acute urinary suppression managed conservatively with 85 per cent survival. Bull[4] mentions eleven conservatively treated patients with 65 per cent recovery. Of even greater importance than these mortality statistics is the observation that in these three combined series totaling fifty-two patients managed conservatively, only one death could be attributed to the retention of solutes. This resulted from hyperkalemia in patient N.B., and there is every reason to believe that this fatality today might have been prevented by cation exchange resins. The remaining deaths were caused by severe coexisting physiological disturbances in other systems of the body and probably could not have been prevented by

dialyzing techniques or other procedures directed at the alleviation of azotemia.

In this connection it is of interest that simple supportive measures are capable of sustaining life for a period of more than fifty consecutive days of urinary suppression. One patient (G.M., Table II) has been reported in detail previously.[1] She lived for forty-nine days with a urinary output of less than 200 cc. on any one day, and for thirty-one days there was absolutely no excretion of urine whatever. Complete uretero-pelvic obstruction due to bilaterally aberrant renal arteries and veins was the cause of suppression in this instance.

Comments

The conclusion seems warranted that acute urinary suppression can be managed successfully by a conservative program simple in approach and technique. Meticulous attention to proper fluid balance, the fulfillment of minimum caloric requirements by carbohydrate administration, and the correction of electrolyte abnormalities with cation exchange resins form the basis of a medical regimen that will tide the large majority of patients over the critical anuric phase of their disease until spontaneous diuresis and recovery set in. The results of this treatment indicate a survival rate of approximately 80 per cent. Such deaths as occur are usually caused by pathology in other systems of the body. If elaborate dialyzing procedures are to occupy more than an experimental place in the management of acute urinary suppression, the proof of their worth must be demonstrated from results that cannot be achieved by conservative measures alone.

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TWENTY-FIFTH GRADUATE FORTNIGHT

THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York

HORMONES IN HEALTH AND DISEASE

OCTOBER 6-17, 1952

SCHEDULE OF MORNING PANEL MEETINGS AT THE ACADEMY
11:00 A.M. — 12:30 P.M. — Room 20 — Wednesdays and Fridays

FIRST WEEK

Wednesday, October 8

Subject: PRACTICAL CONSIDERATIONS REGARDING REALISM AND WISHFUL THINKING IN ENDOCRINE THERAPY

Chairman: Rustin McIntosh

Members: Charles L. Buxton, Martin Perlmutter, Joseph W. Jailer, Ephraim Shorr, Lawson Wilkins

Friday, October 10

Subject: PRACTICAL CONSIDERATIONS REGARDING THE USE OF ACTH AND CORTISONE

Chairman: Louis Leiter

Members: Henry L. Barnett, Arthur W. Grace, Joseph J. Bunim, O. H. Pearson, Louis J. Soffer

SECOND WEEK

Wednesday, October 15

Subject: PRACTICAL CONSIDERATIONS REGARDING DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN DISORDERS OF THE THYROID GLAND

Chairman: David P. Barr

Members: Wm. Barclay Parsons, Cyrus C. Sturgis, J. E. Rall, Sidney C. Werner

Friday, October 17

Subject: PRACTICAL CONSIDERATIONS REGARDING HORMONAL MANAGEMENT OF MALIGNANT NEOPLASMS

Chairman: C. P. Rhoads

Members: Ira T. Nathanson, Rulon W. Rawson, James J. Nickson, W. W. Scott, Willet F. Whitmore, Jr.

THE USE OF THE ARTIFICIAL KIDNEY IN THE TREATMENT OF UREMIA*

JOHN P. MERRILL

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THE use of an apparatus which employed an artificial membrane for the dialysis of blood outside of the body was first suggested in 1913 by Abel, Rowntree, and Turner[1] who employed a device which utilized, for its dialyzing membrane, collodion which these workers extruded themselves. Employing hirudin, the anticoagulant principle of the leech, they successfully performed a number of dialyses in animals. Because of the many technical difficulties involved, attempts to reproduce such a device were sporadic until the generalized use of a better dialyzing membrane in the form of cellophane and an improved anticoagulant, heparin. Kolff in 1944[2] developed what must be considered the first clinically successful apparatus. Other workers in Europe and in Canada shortly published their results with dialyzers of different construction conceived independently. Within the last few years, in this country particularly, the use of the so-called "artificial kidney" has increased, and its potentialities as well as its limitations have begun to be realized through larger experience. All of these devices, though they vary somewhat in design, function by causing blood from the animal or patient to course through a cellophane tube or between two cellophane sheets. On either side of the cellophane membrane is opposed a dialyzing bath appropriately formed with regard to its electrolyte and osmolar composition. The cellophane membrane is impermeable to molecules with molecular weights of about 20,000 or over so that the serum proteins are retained and larger amino acids pass slowly, if at all. The smaller molecules including metabolites such as urea, phosphates, sulfate, and potassium diffuse easily through the pores of the cellophane and are removed in the rinsing fluid on the other side. Since the concentration of essential electrolytes in the bath is such as to affect no gradient

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From the Department of Medicine, Harvard Medical School, and Medical Service, Peter Bent Brigham Hospital, Boston, Mass.

TABLE I

H.M. ♀ 30 *Acute Anuria*

	0 HOUR	6 HOUR
BUN	313	65
Na	135	145
K	9.0	5.2
Co_2	13.5	16.5
Cl	97	115
P	3.13	1.20
SUGAR	145	135
Hct.	32	31
BATH UREA NITROGEN		87 GMS.

for these across the membrane, there is no net exchange of these substances and thus no change in the serum concentration. It is possible, however, if one wishes to remove potassium, for instance, to eliminate potassium from the dialyzing bath, thus creating a marked diffusion gradient from blood to bath, and causing a rapid passage of potassium into the bath where it can be removed, with the resultant depletion of the potassium content of the plasma. On the other hand, if the plasma level of sodium is lower than that in the bath fluid, an influx of sodium into the plasma occurs from the bath as a result of this gradient, and this may occur at the same time that potassium is moving in the opposite direction. Since the individual diffusion gradient for each of these ions determines the direction of its movement and the rate of its exchange, sodium may be added to plasma at the same time that metabolites are removed (Table I). The fact that such transfers may be effected across an inert membrane and in accord with relatively simple physical chemical laws gives the artificial kidney an advantage over techniques such as intestinal irrigation in which the membrane involved is governed by more complicated metabolic processes involving selective resorption and transfer.

Progress in construction of artificial kidneys has involved primarily the use of non-wetable and disposable plastics which have obviated the previous difficulties of clotting and pyrogen reactions, and have made the procedure of hemodialysis in proper hands a relatively safe and, certainly, effective technique. It should be emphasized, however,

that the apparatus itself is only one, and perhaps the smaller part of the technique, the other being the experience, skill, and plain common sense of the operator. These requirements have been adequately fulfilled in a number of laboratories employing this technique, and the experience accumulated to date in the use of the artificial kidney in the treatment of uremia has been uniform and satisfactory enough so that its role as a therapeutic device may perhaps be delineated. Technique of procedure and construction of various apparatus has been recently reviewed.[3]

Clinical Use

1) *Acute Renal Insufficiency*: As early as 1923 it was first suggested that an artificial kidney might be used to maintain life and reasonable well-being during periods of acute renal insufficiency where the underlying lesion was reversible.[4] This view was entertained when the apparatus was first developed at the clinical level, and certain points may now be made with regard to its employment in such cases. There can be no question but that the conservative management of acute renal insufficiency has progressed with recent knowledge to the point where the unwarranted mortality in this syndrome has been reduced to a minimum.[5-7] A young, previously healthy individual without concomitant trauma, sepsis, or vascular disease may survive periods of complete urinary suppression as long as three to four weeks. Our experience with acute renal failure includes a series of 112 patients about half of whom have been treated with conservative measures. The experience with the undialyzed patients fits well with the figures given by advocates of conservative therapy alone. It cannot be too strongly stressed, however, that provided the criteria mentioned for its use above are fulfilled, the artificial kidney is an effective adjunct to such forms of conservative therapy. To argue whether dialysis is "necessary" in the treatment of acute renal insufficiency or whether it changes the mortality rate is pointless in this view. If one considers the case of a 22-year-old man, previously in good health, who became suddenly anuric as the result of intravascular hemolysis, the reason for this statement is perceived. This patient who had no concomitant disease would undoubtedly have survived his ordeal with or without dialysis; however, on the ninth day of his anuria, he was semicomatose, apathetic, and vomited frequently. The required fluid and calories had to be administered carefully by vein. Dialysis with the artificial kidney was accomplished on this day,

and the following morning the patient was able to sit up in a chair, was alert, and responsive, and in spite of continued anuria for another five days, was able to take his entire caloric and fluid requirement by mouth. Diuresis supervened, and he went on to get well as, indeed, he would have with or without the artificial kidney. There can be no question but that the procedure was not "necessary" in this case. There can be no question either, however, but that the conservative management of this problem was greatly facilitated by the procedure. This patient's morbid state was entirely due to retention of normally excreted metabolites. In such a situation, the artificial removal of these metabolites, if it can be accomplished safely and effectively, is a rational approach to treatment. Let us now translate this man's illness into terms of an elderly, obese, hypertensive, arteriosclerotic woman who had become anuric during the course of an operation for the removal of an infected gall-bladder. On the fifth day of her anuria, in part as a result of increased protein catabolism secondary to operative trauma and sepsis, and in part due to the susceptibility of an elderly patient to the toxic effect of these metabolites, the picture was entirely different. The patient was comatose, immobile and heir to all the postoperative complications that an elderly, obese patient with vascular disease may incur if immobilized for too long. Under such circumstances, we have seen dialysis with the artificial kidney improve the clinical state to the point where mobilization is possible, and where the patient can eat and be out of bed. Granting that even in this case survival is possible without the use of artificial means, common sense dictates that where facilities for its employment exist, they should be utilized.

Even with the best conservative measures, however, one can often not predict when diuresis will occur. Equally important, one cannot predict, particularly in the case of the postoperative or the septic patient, when lethal complications, such as acute spontaneous potassium intoxication, may supervene. The syndrome of potassium intoxication which may result from the accumulation of potassium liberated in the course of protein catabolism or shifted from the normal intracellular position under the influence of severe uremia or acidosis is not a universal complication of acute renal insufficiency. It is, however, one which is frequently overlooked, and one which may be lethal during the course of an otherwise reversible disease process. Many methods have been proposed to decrease the extracellular levels of potassium in the anuric

patient. These include the use of glucose and insulin solutions[8] and the use of ion exchange resins.[9] The former is a temporary measure whose duration is short and whose clinical application involves the infusion of extra fluid which may be unwise. The latter, while more effective and highly successful in some cases, in our hands has been variable and unpredictable in its results. Lavage of the various portions of the gastrointestinal tract and of the peritoneal cavity are perhaps more effective in removing potassium but certainly more cumbersome than the previously mentioned methods. The artificial kidney which is certainly as cumbersome has, however, the advantage of not only removing potassium rapidly but of also effectively correcting the underlying chemical disorder which unquestionably facilitates a syndrome of which a high extracellular level of potassium is only one part. In such cases, the use of hemodialysis may perhaps be truly "necessary."

2) *Chronic Renal Insufficiency*: Recent experience with hemodialysis has indicated that the artificial kidney may be of pronounced therapeutic benefit in selected cases of chronic uremia. It should be emphasized that such cases, however, must be carefully selected. In many cases of chronic renal insufficiency, the clinical picture is complicated by hypertensive cardiovascular disease. Hemodialysis corrects only chemical abnormalities, and if the patient's situation depends largely upon derangement of his cardiovascular apparatus, the restitution to normal values of serum metabolite concentrations will affect the clinical picture very little. On the other hand, a prominent feature of most advanced cases of uremia, both chronic and acute, is anorexia, apathy, and, particularly, nausea and vomiting. These appear in large part to be due to retention of metabolite, and the removal of metabolite by hemodialysis effects a decided improvement in these symptoms. At the present time, the therapeutic objective of any form of treatment of chronic uremia is aimed at the amelioration of such symptoms, and if an adequate trial of conservative therapy fails to achieve this result, dialysis may be employed. At first glance, the results obtained might seem to defeat the purpose for which the procedure is employed. In the patient with chronic renal insufficiency, obviously no change in the functional status of the kidneys is accomplished. Thus, removal of non-protein nitrogen is followed at the termination of dialysis by a progressive increase in plasma concentrations to predialysis levels. If this were all that might be accomplished, there would be very little rationale in employing the procedure

for the treatment of chronic uremia. It is of interest, however, that the clinical improvement effected may outlast by weeks and months the return of abnormal serum concentrations of metabolite and electrolyte to predialysis levels. Of even more interest is the fact that unlike the patient with acute renal insufficiency, in whom dialysis may effect marked clinical improvement within hours, the patient with chronic uremia shows little or no effect from the procedure for a period of one to three days. This clinical improvement may then begin in spite of return of abnormal plasma concentrations of non-protein nitrogen, and the sense of well-being may persist far beyond the re-establishment of predialysis values for these concentrations. Teleologically one might suppose that the compensatory mechanisms which adjust for increasing uremia must be reset following the rapid changes in this essentially chemical illness, and that these compensatory mechanisms, set for a new internal milieu, might reasonably be expected in chronic illness to require days rather than hours to adjust. Whether or not such arguments are valid, in many cases this delayed therapeutic response may be compatible with months and in a few cases, years of relatively comfortable and productive existence. It should also be emphasized that a metabolic state, however abnormal, which has been attained slowly over a period of years may entail some degree of risk if it is corrected within a matter of hours. Thus, although the literature tends to emphasize the efficacy of apparatus for hemodialysis, it may well be that the correction of the chronic uremic state should be achieved with an apparatus less effective over a period of days rather than hours.

In general, the polyuric normotensive patient responds better and for a longer period of time than does the relatively oliguric hypertensive uremic patient, and at the present time it can be stated with some degree of surety that the chronic uremic patient with a urine volume of better than 1500 ml./day who has no hypertension and whose nausea, vomiting, anorexia, and weakness fail to respond to conservative measurements may expect a good response to hemodialysis. Responses to successive procedures, unfortunately, tend to be less successful. This may be in part due to the advent of the hypertensive phase of the disease or to the general clinical deterioration. The oliguric response which followed hemodialysis in the chronic uremic with hypertension has been largely abolished by the expedient of dialyzing such a patient against an isourea bath. In such cases, the fact that failure to change the level of the blood

urea nitrogen has made little or no difference in the clinical improvement is a fact of some physiologic significance.

Not the least important responsibility of the physician in the use of the artificial kidney for the treatment of chronic uremia is the necessity for carefully explaining to the patient's family the limitations of the procedure and exactly what is to be expected. It is of paramount importance that the responsible member of the family be fully cognizant of the ends to be attained and the results to be expected. A tragic by-product of this technique is the raising of false hopes with subsequent disappointment and disillusionment.

The clinical improvement, however temporary, may be of importance in preparing a patient with chronic renal insufficiency for surgery aimed at the improvement of his underlying disease. In such cases, pre-operative dialysis may enable him to tolerate a major operative procedure which might otherwise carry considerable risk. In the post-operative procedure, too, once the danger of bleeding with heparin administration is passed, convalescence of the uremic patient may be facilitated. In the same manner, patients with exacerbations of chronic glomerulonephritis or of chronic pyelonephritis may be tided over these periods of crisis, and enough renal function remain to permit reasonably comfortable existence.

Contraindications to Hemodialysis

The recognition of lack of indication for hemodialysis is equally important as the knowledge of indications for the procedure. Uremia, per se, that is, abnormality of plasma concentrations, is not an indication for the procedure unless accompanied by clinical symptoms. Indeed, there is some evidence that disturbing a patient nicely compensated in the chronic uremic state may be a definite form of mistreatment. Similarly, as has been mentioned above, if the clinical state cannot be closely related to the chemical imbalance, the use of the artificial kidney has no value. At the present stage of our knowledge, hypertensive cardiovascular disease or nephrotic edema cannot be treated by hemodialysis. Anuria per se is obviously not an indication for the use of the artificial kidney. If marked symptoms appear or if the medical management becomes difficult because of deterioration of the clinical state, the procedure may be used with some justification. It does nothing, however, for the anuric state in itself and should not be used unless these criteria apply. Similarly,

elevation of blood urea nitrogen, the occurrence of acidosis or hyponatremia in a surgical patient with generalized peritonitis or acute pancreatitis do not entitle one to expect that correction of the chemical abnormalities by dialysis will markedly alter the clinical problem. Although in over 270 clinical trials to date, we have not seen a death attributable to the procedure itself, there are definite contraindications to its application. The first of these stems from the necessity for heparinizing the patient in order to prevent coagulation of the blood during its circuit outside the body. Oozing or bleeding particularly from the gastrointestinal tract may become aggravated during the procedure and fail to cease following its termination, even though the clotting time is restored to normal with protamine. Similarly, subarachnoid hemorrhage or intracranial bleeding of other etiology may be considered probable contraindications to the procedure. Patients with acute glomerulonephritis, particularly with severe hypertension, do not respond well to hemodialysis. The hypertension may be aggravated and convulsions ensue following the procedure, and in such cases, it should be reserved until such time as the chemical deterioration appears to outweigh these considerations. In one case in which anuria followed shock incident to myocardial infarction, dialysis with the artificial kidney resulted in return of the shock-like state. This experience has led us to believe that anuria following acute myocardial infarction should not be treated with the artificial kidney.

Summary

Certain of the uremic states respond with gratifying clinical improvement to dialysis with the artificial kidney. In acute renal insufficiency, the procedure, if properly employed, may be a valuable adjunct to conservative management and occasionally in acute spontaneous potassium intoxication have a distinct advantage over other methods of treatment. The chronic uremic patient whose debility is due primarily to retention of metabolite may improve dramatically though temporarily following the procedure. Where the clinical situation is not in large part due to these derangements, hemodialysis should be expected to have very little effect upon the clinical course. In any consideration of the benefits to be achieved by this procedure, an understanding of the lack of indication and the contraindications are of utmost importance.

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NOTICE

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The Friday Afternoon Lecture Series which have been presented at The New York Academy of Medicine for the past 26 years will be discontinued.

Beginning in November 1952, a series of

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

will be presented

Dates, subjects and panel members will be announced later.

ETIOLOGICAL FACTORS IN CEREBRAL PALSY*

GEORGE G. DEAVER

Professor of Clinical Rehabilitation and Physical Medicine, New York University College of Medicine and Director, Lenox Hill Hospital Cerebral Palsy Clinic

CEREBRAL palsy, by definition, indicates a condition caused by pathology to the motor control of the brain. The neuromuscular manifestations may be spastic or flaccid paralysis, weakness, incoordination or ataxia.

HISTORY

The story of those having cerebral palsy is one of children being hidden away in the home as a curse on the family or sent to mental institutions. Medieval mosaics, monuments and paintings give evidence that cerebral palsy was known many long years ago.

It was not until 1862 that William John Little, an English surgeon wrote a monograph describing the condition which we now call cerebral palsy. The spastic grimacing, drooling child with a "scissors gait" that Dr. Little described gave the erroneous impression that all children with cerebral palsy were of that type and feebleminded. The term Little's disease should not be used to describe all children with cerebral palsy since we know that impaired intelligence does not necessarily accompany the motor disability and that spasticity is only present in one type of cerebral palsy.

INCIDENCE

It is difficult to give the number of children having cerebral palsy. Surveys have always revealed that the number in any given area is always greater than the number reported; that the incidence is not affected by economic, social or geographical factors, and since the condition does not occur in epidemics the number of cases occurring is approximately the same from year to year.

On the basis of repeated samplings, Dr. Phelps estimates that at a

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birth rate of twenty-three per thousand live births, seven cases of cerebral palsy are born each year in each 100,000 of the total population. One of these children dies before the age of six. Using this formula, it is estimated there are 104,895 cerebral palsied persons in New York State up to thirty-five years of age.

The survey made by the New York State Health Department verified Dr. Phelps' estimates that one infant in every two hundred births shows the clinical signs of cerebral palsy.

Etiology

There are certain predisposing factors related to cerebral palsy. It occurs more frequently in premature children, the first born and those with heavy birth weights where prolonged labor is more frequent. It likewise occurs more often in infants of older women, and in boys more frequently than in girls. Older women, on the average, have heavier babies, and boys, on the average, weigh more than girls at birth. Cerebral palsy seems to occur more frequently among white children than colored and this may be due to the average smaller size of the colored new-born and the lower incidence of the Rh negativity in the colored race. With these exceptions there seem to be no economic, social or geographic predilections for cerebral palsy.

The *Prenatal* causes may be due to hereditary or congenital factors. The *hereditary* causes of cerebral palsy may be due to anomaly of the germ plasm resulting in abnormal development of the fetal brain. The *congenital* or *nonhereditary* factors which may cause cerebral palsy are as follows:

1. *Anoxia.* Anything that interferes with placental circulation is a potential cause of anoxia. The brain, primarily the basal nuclei and their connections, are highly sensitive to the lack of oxygen; compression of the cord between the head and bony pelvis or kinks in the cord, could prevent adequate circulation to the fetal brain. Threatened abortion, bleeding during pregnancy or premature separation of the placenta is frequently found in mothers giving birth to cerebral palsied infants.

2. *Maternal Infectious Disease.* Any maternal infection, especially with a neurotrophic virus, may involve the fetal brain. German measles during the first three months attacks the brain of the fetus with great regularity.

3. *Maternal Metabolic Disease.* One of the most frequent causes of prenatal intracerebral hemorrhage is toxemia of pregnancy. The fetal blood vessels in the brain are affected by substances in the mother's blood vessels with death of brain tissue and secondary hemorrhage. Toxemia of pregnancy predisposes to prematurity. Maternal diabetes may cause injury to the fetal brain. Diabetic mothers usually have infants with excessive birth weights and more frequently develop toxemias of pregnancy.

4. *Erythroblastosis Fetalis.* Rh refers to an additional blood factor which is present in 85 per cent of the white population. When an Rh negative woman bears an Rh positive child, the mother often develops anti-Rh positive antibodies which cause a typical form of cerebral palsy. Only one of approximately thirty-three children born to Rh negative women develops erythroblastosis fetalis. The reason for this small number is that the first born is not affected, the first born are more plentiful than the second born and a certain number of the children born will themselves be Rh negative.

The result of Rh incompatibility of the parents often produces kernicterus or neonatal nuclear jaundice of the brain. As a result of the anemia and damage to the liver there is interference with the nutrition of the brain, usually the basal nuclei. When this area is damaged the athetoid type of cerebral palsy occurs often associated with deafness and paralysis of the eye muscles.

The *Natal Causes* of cerebral palsy may be due to 1) anoxia; 2) blockage of the respiratory passage causing asphyxia; 3) analgesia; 4) trauma due to cephalopelvic disproportion and delivery of the breech before the head and forceps; 5) sudden changes in pressure; 6) prematurity and 7) low vitamin K level.

1. Anoxia is the most important natal factor. When the placenta separates from the uterus or the umbilical cord is clamped off the child is dependent upon its own lungs. Kinking or pinching of the umbilical cord during the birth process may result in interference with fetal blood supply and thus cause anoxia.

2. *Blockage* of the respiratory passages causes asphyxia. The newborn child may aspirate a great deal of mucous or amniotic fluid in its passage through the birth canal. Such respiratory obstruction must be recognized and removed by suction or by the passage of a tracheal catheter.

3. *Analgesia.* The respiratory center of the infant is much more sensitive to morphine than the adults'. Many mothers who have been given "twilight sleep" have their child born with morphine poisoning. The child breathes very slowly and the pulse is very slow and the temperature low. Because of insufficient oxygen it will be a "blue baby." Obstetrical anesthesia which causes maternal asphyxia may also asphyxiate the fetus. Spinal and caudal anesthesia may lower the systolic blood pressure below 80 in 10 per cent of cases which is sufficient to reduce seriously the oxygen supply to the baby.

4. *Trauma.* Most of the traumatic causes of brain injury at birth may be considered as physiologic. Just being born is a difficult hurdle to pass. In the birth process, the baby uses its head for a battering ram propelled by strong uterine contractions. When the child's head is large and the pelvis small, the natural safeguards which allow the skull to conform to the shape of the birth canal may be insufficient to protect the brain from injury. This is especially true if labor is prolonged and hard. Occasionally too strenuous an application of forceps by the obstetrician, may injure the skull and brain. Contrary to popular opinion, trauma caused by the obstetrician is probably responsible for less than 5 per cent of all cases of cerebral palsy.

In normal cephalic birth the infant can breathe before the blood supply from the placenta is interrupted. When the breech is delivered first, the time between the delivery of the cord and the delivery of the head becomes a potential period of anoxia. Thus, cerebral palsy is much more common in infants born by breech than by cephalic mechanism.

5. *Sudden Changes in Pressure.* The so-called "spontaneous deliveries" and infants delivered by cesarean section which prove satisfactory to the mother, are not free of complications associated with brain lesions. The intrauterine pressure is greater than atmospheric pressure. A sudden change from the former to the latter may result in sudden release of pressure with resultant air emboli, ruptured blood vessels and hemorrhage. In both instances there may be insufficient time to allow for natural decompression.

6. *Prematurity.* A premature baby has much thinner blood vessels than the full term mature child. The weak blood vessel walls will tend to predispose this infant to cerebral hemorrhage.

7. *Vitamin K.* Sometimes a child is born with a tendency to bleed. This neonatal bleeding may be due to a lack of vitamin K in the blood.

By giving vitamin K to the mother while she is in labor, she in turn will transfer it to the child. This condition used to be responsible for about one per cent of the cases of cerebral palsy.

The *Postnatal* causes of cerebral palsy result from brain pathology after birth. The principal causes are trauma, infections, neoplasms, drugs, vascular conditions and anoxia. It is estimated that there are over one million patients with acquired cerebral palsy of the spastic and flaccid hemiplegia type as a result of cardiovascular accidents. This number increases with our life expectancy.

Discussion

Cerebral palsy is difficult to diagnose in the infant and very young child. By obtaining a careful family history in our cerebral palsy clinics for children, efforts are made to discover the indications for suspecting brain damage.

The developmental history of the child often indicates brain pathology. Gessel and Amatruda have listed the periods in which infants perform certain movements. The failure of the child to follow the developmental maturity scale is often the only early indication of brain damage. If a baby cannot lift his head upwards from the prone position for short periods during the first weeks, kick both feet together instead of a reciprocal pattern, or holds his hands in a closed position after sixteen weeks, or is delayed in sitting, standing and walking beyond the normal periods, it must be regarded as a significant sign of central nervous system impairment.

Conclusions

The number of infants born with cerebral palsy, which is one in every two hundred live births, can only be reduced in so far as we are able to control the predisposing factors, and the prenatal and natal causes.

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CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

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ABSTRACTS

*Fibrinolytic and Anticoagulant Effects of Intravenous Crystalline Trypsin**

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The fibrinolytic property of in vitro trypsin is well recognized. The effect of in vivo trypsin upon the coagulation mechanism, however, requires further elucidation. Massive intravenous doses of trypsin were administered to 65 rabbits and 25 dogs and only slight systemic reactions after primary injection were noted, *if given slowly*. Proteolysis of fibrin and other clotting moieties were consistently observed. Since intravenous trypsin so administered, did not produce serious side effects, we proceeded to determine its effect upon 1) the coagulation mechanism and 2) artificially formed thrombi, in rabbits and dogs.

Intravenous trypsin in a mean dose range of 75 mg/kg produced the following effects upon the protein clotting constituents in rabbits and dogs. There was marked diminution in prothrombin, Ac-globulin, fibrinogen, antifibrinolysin and antithrombin. The bleeding and coagulation times were prolonged. Saline treated control animals showed no significant changes in clotting constituents or coagulation and bleeding time.

Intravenous trypsin had a significant, but variable, lytic effect upon experimentally produced thrombi, using morrhuate, thrombin and thromboplastin. Gross changes in the rabbit ear vein thrombi, following trypsin, included 1) softening, and, in several instances, disappearance of the thrombus in situ, 2) restoration of local circulation, and 3) restoration of vessel wall compressibility. In saline treated controls having clots, these changes were not observed. The microscopic features of trypsin treated thrombi included 1) apparent diminution of fibrin, 2) marked diminution of cellular and platelet masses, 3) no untoward effect upon vessel walls. Saline treated controls showed persistence of a dense fibrin meshwork plus organized homogeneous masses of platelets and cells.

The rate of trypsin administration was of critical importance in rabbit experiments. When administered slowly (8 drops/minute) no untoward reactions were observed. One lot of trypsin was toxic for rabbits but not for dogs. Dogs were given the intravenous infusion much more rapidly (30-40 drops/minute) without deleterious systemic effect. In the light of the massive dosage of trypsin employed in these experiments, the absence of shock was impressive. Trypsin

* The trypsin employed in these experiments was obtained through the courtesy of Dr. Marvin Ziporyn, Armour Laboratories, Chicago, under the trade name "Tryptar."

was then given intravenously to forty-two patients without significant side effects when the infusion rate and enzyme concentration were within specific limits. There was marked improvement observed in eight patients with thrombophlebitis, and twelve patients with ischemic, purulent leg ulcers.

SUMMARY

1. Intravenous trypsin in rabbits and dogs has anticoagulant properties, characterized by proteolysis of prothrombin, Ac-globulin, antifibrinolysin, antithrombin and fibrinogen.
2. When trypsin is administered slowly and cautiously there is remarkable absence of shock, even with large doses (100 mg/kg).
3. The intravenous administration of trypsin in rabbits and dogs has a lytic effect upon artificially formed thrombi, the exact mechanism of which remains to be elucidated.
4. Following intravenous trypsin therapy, 8 patients with thrombophlebitis and 12 patients with ischemic leg ulcers showed marked improvement.

Shortening the Immunization Procedure in Pollen Allergy: Experiments with 101 Ragweed-sensitive Subjects During 13 Years

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While under clinical and immunological observation, a group of 101 patients with pollen allergy were given various types of immunization for periods ranging from two to thirteen successive years. Therapeutic methods included the conventional, preseasonal and perennial injections of aqueous extract given under the skin. Whereas such courses called for eight to forty visits a year, it was found that as much could be accomplished in from four to seven treatments. Even greater restriction was made possible by the experimental use of "depots" of the antigen in the form of water-in-oil emulsions, employing Falba and mineral oil. With this procedure, the allergen could be so gradually released from the depot under the skin or in the muscle that a single, large dose provided immunity comparable to that obtained with aqueous therapy requiring multiple visits. After 287 such depot immunizations, satisfactory clinical results occurred in 63 per cent of trials. This was to be compared with an incidence of 75 per cent which obtained when aqueous treatments had been administered during from four to forty office calls. The lower figure may reflect an ample correction made by us for any contribution of antihistamines to the clinical result of depot therapy. (The conventional courses would have been little affected by this factor since most of them had been given prior to the advent of these drugs.)

Some difficulty was encountered in the early years of depot therapy in that residual indurations at times remained palpable for many months, but this has been obviated by limiting the volume of mineral oil and by avoiding the intracutaneous route. The incidence of overdose reactions was as follows: fifty reactions per 100 courses of plain extract given during from eight to forty visits; twenty-five per 100 courses of extract completed in four to seven visits, and seventeen per 100 courses when a depot was injected. Most of the latter were of mild intensity. No abscesses or fatalities were associated with depot treatments. It is felt that the depot procedure warrants further development because of its practical aspects. Used in conjunction with the threshold, conjunctival test which serves as a guide to the patient's tolerance for antigen, it carries a risk little greater than that of conventional management.

Treatment of Pernicious Anemia with Massive Parenteral Doses of Vitamin B-12

EDWARD H. REISNER, JR. and LEO WEINER

In the hope of obtaining prolonged remissions, fourteen patients with pernicious anemia in relapse were treated at weekly intervals with single injections of 1,000 mcg of vitamin B-12 and followed through remission to subsequent relapse with no further therapy. Nine patients had remissions lasting three (3), four (1), five (2), six (2) and seven months, respectively. Four patients were lost from follow-up after four, six, eight and nine months, at which time they were all still in remission. One patient failed to show complete remission following the injection and developed an exacerbation of cord disease two months later.

Seven patients with chronic combined system disease due to pernicious anemia, who had been studied for several months or more and were felt to be stabilized on conventional therapy, were treated with weekly injections of 1,000 mcg of vitamin B-12 for periods of four, six, seven, nine, ten (2) and thirteen weeks. In none of these patients was any improvement observed that might not have been expected with conventional doses of B-12 or liver extract.

Urinary excretion studies on patients with pernicious anemia in relapse, receiving injections of 100 to 1,000 mcg of vitamin B-12, showed that from 51 to 98 per cent of the injected dose was recoverable from the urine in the succeeding seventy-two hours.

The failure of the massive doses to produce consistently longer remissions is attributed to the fact that most of the massive dose is excreted. In view of this fact it is felt that parenteral doses of more than 50 mcg of vitamin B-12 are largely wasted, and therefore of no advantage over the smaller doses in the treatment of pernicious anemia.

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Cortisone Therapy of Urticaria

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It has been noted by other observers that cortisone and corticotropin effectively control acute urticarial reactions due to antibiotics, particularly pericillin and aureomycin. But there have been no specific series of cases presented to demonstrate particular attributes of these hormones. Previous observations have been embodied as parts of other studies. Treatment of this type of case has constituted the conventional repeated small dosages of corticotropin.

The cases to be presented in this series will show the effective control of acute urticarial reactions to penicillin by means of administration of a single injection of 50 to 100 mg. of cortisone.

The treated cases will demonstrate response to treatment within 24 to 48 hours. Results of treatment and dosage will be presented.

The management of acute urticarial reaction to penicillin by cortisone will be outlined. Instances will be given in which cases did not respond to corticotropin but showed excellent involution with cortisone.

The theory and rationale for the effectiveness of cortisone in antibiotic allergic reactions will be discussed. Caution in the use of these hormones in other types of benign dermatoses will be urged.

The Occurrence of "Spontaneous" Infections After the Administration of Cortisone and ACTH

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The frequency of intercurrent infections in patients treated with cortisone or ACTH is becoming increasingly important. This is not entirely unexpected since it had been reported that a large percentage of mice receiving cortisone develop spontaneous infections with ordinarily "non-pathogenic" bacteria which are normally present in the nasopharynx or gastrointestinal tract. Control animals, not receiving cortisone, were not susceptible to such infections even when placed in the same cage with infected animals.[1] From these findings it was apparent that infections would be frequently encountered, and that these infections were dependent upon a cortisone-mediated exhaustion of immune bodies and other protective mechanisms.

Isolated cases of the human counterpart of this physiopathologic state in the experimental animal have been frequently reported. Two cases of Hodgkin's disease and two of myeloid leukemia treated with cortisone or ACTH are considered in this paper. In both Hodgkin's disease cases, extensive fungus infection was found at autopsy. The organisms were identical morphologically and in one case it was identified in culture as Aspergillus niger. One patient with leukemia died of lobar pneumonia showing gram-positive cocci in macrophages, and the other developed E. coli sepsis and a duodenal ulcer containing Monilia albicans.

These "spontaneous" infections occurring in patients receiving cortisone or ACTH may be either reactivated subclinical infections which were present in dormant reservoirs before therapy was instituted, or new infections by "non-pathogens" taking root in hosts with exhausted defense mechanisms.

The clinical effects of cortisone are due in part to a depression of antibodies with consequent amelioration of pathologic states resulting from antigen-antibody reaction, since sufficient antibody is no longer available for these reactions. This same depression of antibody also deprives the host of those immune bodies which offer a major resistance to the unrestricted multiplication of microorganisms. In the absence of the bacteriostatic effect of these antibodies, bacteria which ordinarily are non-pathogenic multiply at a rapid rate and at times form colonies as though they were growing in enriched culture media. Thus the same influence of cortisone (or ACTH) on antibody has both beneficial and deleterious effects: on the one hand beneficial, by obviating antigen-antibody reactions and on the other deleterious, by depressing protective mechanisms including antibodies.

In instances of spontaneous infection in which x-ray or nitrogen mustard was administered, the role of these agents, which have effects similar to those of cortisone and ACTH, must likewise be considered as must also the role of antibiotics. In addition, in cases of Hodgkin's disease in which reports of tuberculosis or fungus infections are not uncommon, there is considerable discussion of the coincidental, symbiotic or causal relationship of the organisms. The occurrence of "unexpected" infections after cortisone or ACTH administered in maladies such as these raises similar questions.

Because of the frequency of infection, it is a standing procedure in this laboratory to smear and culture the tissues from cases receiving cortisone or ACTH.

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*The Effect of ACTH and Cortisone on the Tuberculin, Dick, and Schick Tests in Essentially Normal Young Men**

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Inhibition of the tuberculin test in man by ACTH and cortisone has been reported by several observers.[1-3] During an investigation of the effects of ACTH and cortisone at Osaka Army Hospital, Japan, on the healing of frostbite lesions, we observed the response of these subjects to the tuberculin, Dick and Schick tests.

The details of intravenous ACTH and oral cortisone therapy are described elsewhere. Satisfactory evidence of adrenocortical stimulation was obtained.[4, 5]

Second strength tuberculin (Purified Protein Derivative) was injected intradermally on the twenty-fifth day of hormone administration. The reactions were measured and classified as negative or positive (1 to 4 plus). Positive reactions were demonstrated in the ACTH group by nine of thirteen subjects (69 per cent); in the cortisone group by fifteen of twenty-two subjects (68 per cent); in the control group by seventeen of twenty-six subjects (65 per cent). There was no significant difference between the groups in the degree of positive reaction. After cessation of hormone therapy all the negative reactors were retested. No significant change in reaction was observed.

In the Dick and Schick tests diluted toxin was injected intradermally in one forearm and a control solution in the other arm. Reactions were measured and classified as negative with or without pseudo-reaction and positive with or without pseudo-reaction. We observed no significant differences in reaction in the ACTH and cortisone groups as compared to the control group.

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*The Relationship of the Ulnar Styloid Process to Disabilities of the Wrist Joint Following Colles' Fractures**

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Following Colles' fractures, patients more frequently than not complain of pain, weakness, and disability of the wrist joint; and many who perform manual labor have to wear adhesive strapping or wristbands for support. The disability is particularly severe in individuals whose occupations demand gripping, lifting, and twisting of the hand and wrist.

Cadaver studies indicate that the instability and weakness are due to the release of the stabilizing influence of the ulnar collateral ligament at the time the ulnar styloid process is fractured. Although such a fracture is by definition a part of Colles' fracture, little attention in the past has been given to the treatment of the styloid process at the time the major fracture in the radius is being treated.

It is most important, therefore, to gain reduction and to obtain union of the ulnar styloid process. When such treatment fails and luxation of the ulna occurs, surgery is necessary to re-establish stability to the radioulnar joint.

The new operative procedure for this condition consists of a 6 cm. incision being made over the dorsal aspect of the distal radioulnar joint. The incision is longitudinal because it gives a better exposure and because, being proximal to the wrist joint, no skin creases are crossed. The extensor digitorum communis and extensor indicis proprius tendons are retracted laterally, while the extensor carpi ulnaris and extensor digiti quinti proprius tendons are retracted medially. The dorsal carpal ligament is partially incised. The soft tissues overlying the radioulnar joint are incised transversely and reflected proximally, to produce a flap to cover the fascia at the completion of the fascial transplant. Six drill holes are placed in the two bones. The holes are three millimeters in size, and are drilled only through the posterior cortices, those in each bone being connected to each other through the cancellous portion. The first drill hole is placed in the head of the ulna near the lateral border and just proximal to the cartilaginous rim which covers the distal one-half of the distal end of the ulna. The second hole is placed in the neck of the ulna, one centimeter proximal to the first hole. Two holes are placed in the medial border of the radius on a level opposite the two holes in the ulna, and two additional holes are placed farther laterally. Thus, four drill holes are placed in the radius and two in the ulna, the extra two holes being used to gain greater purchase on the fascia so it may be sutured under firmer tension and away from the articulation rather than directly at the joint where looseness and relaxation occur.

An 18 cm. strip of fascia is removed from the thigh and started through the most distal and lateral drill hole of the radius and brought out through the corresponding medial hole. It is passed across the radioulnar joint into the proximal drill hole of the ulna and out through the distal hole of the same bone; then back across the joint to the most proximal and medial hole of the radius, and out through the corresponding lateral hole. With the forearm held in neutral rotary position, the fascia is drawn taut and sutured to itself across the two most lateral holes of the radius. The fascia thus produces an x-shaped ligament, not through the joint but across the external aspect of the articulation. Lastly the transverse soft tissue flap is brought distally across the fascial transplant, the tendons

* From the Department of Surgery (Orthopedics) of the New York Hospital-Cornell Medical Center. This study was aided by a grant from a charitable trust.

are replaced in their grooves, and the dorsal carpal ligament is sutured. A forearm circular plaster cast is applied from the metacarpophalangeal joints to the elbow, and worn for six weeks.

Inasmuch as the operation has been found satisfactory in all respects no attempt to date has been made, in the chronic cases of nonunion, to try to obtain bony fusion of the ulnar styloid process.

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*Dynamic Changes in Acid Base Balance During Anesthesia**

D. A. Holaday, D. Ma and E. M. Papper

Recent studies have called attention to the development of respiratory acidosis during thoracic surgery. Preliminary observations have been completed on 40 patients in the Presbyterian Hospital to determine the time course of the changes in acid-base balance which occur during the period of anesthesia and operation. pH determinations were made on arterial blood at body temperature with a potentiometric instrument. This device permits direct introduction of blood from an arterial needle into a glass electrode through a fine bore tubing at intervals as frequent as every two or three minutes. Carbon dioxide and oxygen contents of blood samples, drawn at hourly intervals, were determined manometrically; pCO_2 and buffer base deficit were calculated and plotted against time.

The changes of pH and pCO_2 incurred during intrathoracic operations, during which respiration was assisted by manual compression of the rebreathing bag, averaged almost twice those observed during abdominal procedures during which spontaneous respiration was permitted. The smallest deviations from preoperative values occurred when a mechanical respirator was used. Extreme CO_2 retention occurred most frequently during the period of induction and tracheal intubation. Significant reductions in oxygen saturation of hemoglobin were rarely seen.

Two distinct patterns of metabolic acidosis were distinguishable. The first developed most notably during prolonged ether anesthesia. It progressed slowly but to extreme degrees, exceeding 13 milliequivalents per liter in two instances. Its appearance was unrelated to alterations of ventilation. The second type developed subsequent to, and parallel with periods of respiratory acidosis. Elimination of the deficiency in ventilation was accompanied by correction of the fixed base deficit. The latter was usually small, and never exceeded 6 milliequivalents per liter. Work is in progress to analyze the mechanisms responsible for these reactions.

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*Increased Xanthurenic Acid (4.8 Dihydroxy-Quinoline-2-Carboxylic Acid) Excretion in Normal and Abnormal Pregnancy**

M. WACHSTEIN AND A. GUDAITIS

It is by now well known that vitamin B_6 (Pyrodoxine) deficiency will so alter the intermediary metabolism of Tryptophan as to lead to the excretion of large amounts of Xanthurenic acid (4.8 Dihydroxy-Quinoline-2-Carboxylic Acid) in the urine. Herbert Sprince and co-workers (*Amer. J. Obst. Gynec. 64*:84-92, 1951) have recently shown that following the ingestion of 10 gm. of dl-Tryptophan on the preceding evening, the concentration of Xanthurenic acid was much higher in the morning specimen of patients with toxemia of pregnancy, than in a comparable urine specimen of normal non-pregnant women and women with uncomplicated pregnancy.

In the present study the *total* urinary excretion of Xanthurenic acid for a 24-hour period preceding, and for two 24-hour periods following the ingestion of 10 gm. dl-Tryptophan was determined in healthy men and women, in uncomplicated pregnancy as well as in women with toxemias of pregnancy, and finally in a group of patients with miscellaneous diseases. In all pregnant women the test was started one day after delivery. With only very few exceptions all of the increased amounts of Xanthurenic acid were excreted within the first 24-hour periods following the test dose of Tryptophan. In the first group of ten healthy individuals (six females and four males) the excretion of Xanthurenic acid following the administration of Tryptophan varied between 0 and 25.5 mg. (average 11.3 mg.). In 13 patients with uncomplicated pregnancy the 24-hour excretion following the test meal was found between 70 and 312 mg. (average 194.4 mg.). The corresponding values established in nine cases of toxemia of pregnancy were 84 to 663 mg. (average 295.4 mg.). The last group of twenty patients with various medical diseases excreted Xanthurenic acid in amounts varying between 0 and 74 mg. (average 20.7 mg.). This group included five patients with liver cirrhosis and a history of markedly reduced food intake. Three of these patients showed a moderate rise in Xanthurenic acid excretion (33, 33 and 45 mg. respectively) while the highest value of 74 mg. was observed in a patient with a history of malnutrition and pneumonia. All of the pregnant women, on the other hand, were on a normal, apparently well balanced diet.

The excretion values of Xanthurenic acid observed in pregnant women at term are comparable to those found by L. D. Greenberg and co-workers (*Arch. Biochem. 21*:237-39, 1949) in healthy volunteers on an experimental vitamin B_6 deficient diet. It is therefore concluded that there exists in pregnant women at term a relative, biochemically demonstrable vitamin B_6 deficiency. This deficiency occurs apparently in women with or without toxemia, although the highest excretion values of the abnormal metabolite have so far been observed in women whose pregnancy was complicated by toxemia.

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Continuous Intravenous Drip of Meperidine and Scopolamine for Relief of Pains of Labor*

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The intravenous use of dilute solutions of medicaments is becoming frequent in obstetrics. Several analgesic substances have already been used: Intravenous alcohol by Fetchko and intravenous procain-pentothal during labor by Belinkoff and Trudeau. It seemed to us that the commonly used combination of meperidine and scopolamine might prove to be more efficacious and safer for both mother and fetus when given by intravenous drip method rather than the customary intramuscular route.

Abelson, in our institution, used a single concentrated intravenous dose of meperidine and scopolamine. Winters et al. employed a single dose intravenous injection in the second stage of labor for anesthetic purposes.

Patients were selected at random without regard to age and parity where there were no fetal or maternal complications apparent or expected. When the contractions were active and regular, the cervix dilating and the patient uncomfortable, the intravenous injection was begun.

Two hundred mg. of meperidine and 0.65 mg. of scopolamine were dissolved in a commercially available bottle of 500 cc. of 5 per cent glucose in water. Approximately 200 to 250 cc. of this fluid was administered rapidly so that within 15 minutes a good degree of sedation and analgesia was obtained. The remainder was given at 40 to 60 drops per minute, depending on the response of the patient. No premedication was administered.

There were 25 patients in this series, 15 multiparas and 10 primiparas. Their ages varied from 16 to 38 years. Total amounts of medication given ranged from 140-400 mg. of meperidine and 0.38-1.5 mg. of scopolamine. Total time required was 25 minutes to 6½ hours. Twelve cases were delivered spontaneously, ten by low forceps, and 1 by mid forceps. In a twin pregnancy, the first infant was delivered spontaneously, the second by breech extraction. One case was an assisted breech delivery.

Evaluation of the results was based mainly on the patients' subjective opinions and response. Twenty-two patients reported good or excellent analgesia, while three reported fair effects. There were no poor results. Eighteen had excellent or good amnesia, five reported fair, and two poor results.

No supplementary anesthesia was required for delivery in nine cases. Nine received GOE, two GO, three pudendal block, one pudendal plus GO and one open drop ether.

Twenty-two cases, including the twins, showed no effects on the infants. Three showed slight sluggishness and required mild resuscitation, but in these there were complicating obstetrical and pediatric factors.

Side effects were not serious enough to interfere with the administration of the drug. The most prominent were dizziness, nausea and vomiting. Three patients exhibited excitement.

The desired analgesic and amnesic effects were obtained in the great majority of patients. Emotional patients who resisted a rectal examination were sufficiently relaxed to permit delivery and episiotomy without supplementary anesthesia. The infants were not affected adversely by the medication. Further advantages are that the medication can be given in short, rapid fashion, which is particularly effective with multiparae, and that it can be increased or discontinued at will, according to the needs of the patient.

A disadvantage is the fact that the patient and the rate of flow must be observed constantly. The excitement, which was seen rarely (three cases), was no greater than that seen with intramuscular administration of the same drugs.

We believe that the intravenous drip method of administering meperidine and scopolamine to patients in active labor is a more effective and safer means of obtaining analgesia and amnesia than the intramuscular route. Further investigation is in progress to determine its value more fully.

* Demerol, Winthrop-Stearns, Inc.

*An Experimental Study of Radiation Pneumonitis**

HERBERT LOBSENZ, ARTHUR LEVINE AND DIRAN SEROPIAN

Radiation pneumonitis is a major limiting factor in the treatment of lesions of the lungs and esophagus by high dosage radiation therapy. Inhibition or modification of radiation pneumonitis would permit a more effective means of therapy in pulmonary and esophageal cancers. The object of the investigation, therefore, is to elucidate the possible mechanism by which this syndrome is produced, and to attempt by use of a variety of agents to modify these changes. This report deals essentially with control studies of acute and chronic radiation pneumonitis in young and adult guinea pigs, and a discussion of possible mechanisms involved in its production.

Young and adult guinea pigs were subjected to thoracic irradiation using doses of 100r and 200rD (TSD-50 cms.: 5ma.: 200 KV: ¼ Cu + 1 Al HVL — 0.55 Cu). Histologic changes were noted in the lungs at the end of 24 hours, these consisting mainly of interstitial thickening (edema?), interstitial round cell infiltration, and, in the higher dosage, extravasation of blood into the interstitial and, occasionally, intra-alveolar spaces. These effects occurred despite normal maintenance of other systemic factors determining blood coagulability. The white blood counts were not affected in this acute stage.

In the absence of infection (sterile stab cultures), the lungs, at the end of 30 days, showed remarkable regression toward a normal appearance, with residual hemorrhage, minimal endarteriolar sclerosis, and spotty areas of emphysema. In these non-infected lungs, there was very little residual fibrous scarring.

Abdominal radiation with the thorax protected produced similar changes. The pulmonary changes are not specific for radiation trauma alone and can be reproduced by sudden cerebral traumatic death or intraperitoneal sodium pentobarbital death. The radiated animals showed the greatest frequency of changes described by a significant majority.

A conceivable cause of end-capillary cell trauma could be endarteriolar thrombosis with peripheral anoxemia. Favorable results have been reported in humans with the use of dicumarol. In guinea pigs whose clotting time was minimally doubled by the use of heparin, no protective action was noted—the changes being the same as in those receiving radiation alone.

Since the vascular bleeding changes occurred acutely, without demonstrable changes in the clotting mechanism, it is conceivable that a specific humoral capillary-toxic substance is liberated (peritoneal radiation produced pulmonary changes) in addition to direct pulmonary radiation trauma.

* From the Surgical Research Laboratory, Maimonides Hospital of Brooklyn and the State University of New York, College of Medicine at New York.

*The Estimation of Insulin Sensitivity by the Modified Glucose Insulin Tolerance Test**

SYDNEY S. LAZARUS
AND BRUNO W. VOLK

In a study of the Glucose Insulin Tolerance Test introduced originally by Himsworth for the differentiation of the insulin-sensitive from the insulin-insensitive diabetic, we observed that six of seventeen non-diabetic individuals had an abnormal pattern, although there was no other clinical or laboratory evidence of an endocrine or metabolic abnormality. This is borne out by the differences of opinion regarding the classification of diabetic patients as to insulin-sensitivity by this procedure.

A modification of Himsworth's Glucose Insulin Tolerance Test is therefore introduced, which consists of the administration intravenously of one-tenth unit of crystalline insulin per kilo of body weight 30 minutes after the intravenous injection of 25 grams of glucose in 50 per cent solution. The results obtained by this procedure in 40 non-diabetic individuals showed a homogeneous distribution. The rate of decline of the blood sugar level for the 30 minutes after injection of insulin varied from 2.4 mg/100 ml/min. to 5.7 mg/100 ml/min., with a mean of 3.8 mg/100 ml/min. and a standard deviation of 0.7 mg/100 ml/min.

In the diabetic patients a non-homogeneous distribution of the results was obtained. Seven patients (29 per cent) had values of less than 2 mg/100 ml/min. and those were considered to be insulin-insensitive. Thirteen patients (54 per cent) had values of 2.5 to 5 mg/100 ml/min. and were therefore considered normally sensitive to the action of insulin. The remaining four patients (17 per cent) with rates of decline varying from 2 to 2.4 mg/100 ml/min. could not be assigned to either category.

The non-homogeneous distribution of the results obtained with this procedure in diabetic patients tends to support their differentiation into an insulin-sensitive and an insulin-insensitive group. The ratio of the 30 minute blood sugar level of the modified Glucose Insulin Tolerance Test to the rate of decline of the blood sugar level after insulin which was termed the "sensitivity factor" showed, in general, a correlation with the daily insulin requirement of the patient, so that from this value the amount of insulin necessary for control of the diabetic patient can be predicted within limits.

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* Complete original article published in *The Journal of Laboratory and Clinical Medicine*, 39:404-13, March 1952.

The Council of The New York Academy of Medicine at a regular meeting held November 29, 1950, approved a resolution which established an award to be known as the "Academy Plaque." This award was to be given "in recognition of extra-ordinary services rendered to the Academy, in any of its various departments, functions or services."

The award of the Plaque is not limited to either physicians or Fellows of the Academy but may be bestowed upon "any individual, anywhere."

FIRST AWARD OF THE ACADEMY PLAQUE

AT THE Stated Meeting of the Academy on May 1, 1952, the first award of the Academy Plaque was made to Dr. Orrin Sage Wightman.

Dr. Wightman was elected to Fellowship in the Academy in 1905 and is at present the Chairman of the Board of Trustees.

In the many years of his association with the Academy, Dr. Wightman has rendered numerous and invaluable services to the Academy, to medicine and to the community.

In presenting the Plaque to Dr. Wightman, the President of The New York Academy of Medicine, Dr. Wm. Barclay Parsons, made the following citation:

"It is with the greatest personal pleasure that I now have the privilege of making the first Award of the Academy Plaque. This Plaque, recently established, is to be awarded for outstanding services to the Academy, whenever and to whomever it may be appropriate to do so.

"This first Award goes to one of our Elder Statesmen for his generous giving to the Academy—of heart, of mind, and of substance.

"Of heart, through his unabating enthusiasm and unflagging support since his election to Fellowship forty-seven years ago.

"Of mind, in his critical constructive, and productive contributions to the Committee on Medical Education for seven years, to the Committee on Medical Information which he helped found in 1928 and to which he has been as a tower of strength ever since, and as a Trustee since 1945, serving as Chairman since 1946.

"And lastly of substance, in anonymity.

"Dr. Orrin Sage Wightman, please accept this first Academy Plaque in recognition of your outstanding services in so many ways, for so many years, and as a token of the esteem and affection of the Fellowship of The New York Academy of Medicine."

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EVENING LECTURE PROGRAM

MONDAY, OCTOBER 6

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WM. BARCLAY PARSONS

HORMONES AND COMMON SENSE
LUDWIG KAST AWARD
FULLER ALBRIGHT, *Associate Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital*

HORMONES OF THE ANTERIOR PITUITARY GLAND
ABRAHAM WHITE, PH.D., *Lecturer in Biochemistry, College of Physicians and Surgeons, Columbia University*

THE REGULATION OF WATER EXCRETION BY THE NEUROHYPOPHYSIS
H. B. VAN DYKE, *Hosack Professor of Pharmacology, College of Physicians and Surgeons, Columbia University*

TUESDAY, OCTOBER 7

HORMONES OF THE ADRENAL CORTEX
E. C. KENDALL, PH.D., *The James Forrestal Research Center, Princeton University*

DIAGNOSIS OF ENDOCRINE DISEASE: CLINICAL AND LABORATORY CONSIDERATIONS
LOUIS J. SOFFER, *Associate Attending Physician and Head of Department of Endocrinology, The Mount Sinai Hospital, New York*

WEDNESDAY, OCTOBER 8

THE ENDOCRINE CONTROL OF METABOLISM
FRANK L. ENGEL, *Associate Professor of Medicine and Associate in Physiology, Duke University*

DISTURBANCES IN GROWTH
LAWSON WILKINS, *Associate Professor of Pediatrics, Johns Hopkins Medical School; Director of Endocrine Clinic, Harriet Lane Home, Baltimore*

THURSDAY, OCTOBER 9

MANAGEMENT OF ADDISON'S DISEASE IN ADRENALECTOMIZED PATIENTS
D. M. BERGENSTAL, *Assistant Professor of Medicine, University of Chicago Medical School*

ACTH, CORTISONE AND RELATED STEROIDS IN CLINICAL MEDICINE: PRACTICAL CONSIDERATIONS
CHARLES RAGAN, *Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University*

FRIDAY, OCTOBER 10

PHEOCHROMOCYTOMA WITHIN AND WITHOUT THE ADRENAL MEDULLA
GEORGE F. CAHILL, *Professor of Urology, College of Physicians and Surgeons, Columbia University; Director of Department of Urology, Presbyterian and Francis Delafield Hospitals*

VIRILISM
JOSEPH W. JAILER, *Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital*

MONDAY, OCTOBER 13

CUSHING'S SYNDROME

ABBIE I. KNOWLTON, *Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University*

DIABETES: METABOLIC EFFECTS OF INSULIN

DEWITT STETTEN, JR., *Chief, Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc.*

TUESDAY, OCTOBER 14

THE PITUITARY THYROID RELATIONSHIP IN NORMAL AND DISORDERED THYROID STATES

SIDNEY C. WERNER, *Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital*

CHOICE OF MANAGEMENT IN HYPERTHYROIDISM

CYRUS C. STURGIS, *Professor and Chairman of the Department of Internal Medicine; Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan*

WEDNESDAY, OCTOBER 15

THYROIDITIS AND MYXEDEMA

CARPENTER LECTURE

DAVID P. BARR, *Professor of Medicine, Cornell University Medical College; Physician-in-Chief, The New York Hospital*

PARATHYROIDS AND CALCIUM METABOLISM

I. SNAPPER, *Physician and Director of Medical Education of The Mount Sinai Hospital, New York*

THURSDAY, OCTOBER 16

USE OF THE STEROIDS AND GONADOTROPINS IN GYNECOLOGY

HOWARD C. TAYLOR, JR., *Professor of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University; Director of Obstetrics and Gynecology, Sloane Hospital of the Columbia-Presbyterian Medical Center*

HORMONAL CONTROL OF NEOPLASTIC GROWTH

RULON W. RAWSON, *Attending Physician, Memorial Hospital; Chief, Division of Clinical Investigation, Sloan-Kettering Institute; Professor of Medicine, Sloan-Kettering Division, Cornell University Medical College*

FRIDAY, OCTOBER 17

THE RELATIONSHIP OF HORMONES TO PEPTIC ULCER

JOSEPH B. KIRSNER, *Professor of Medicine, University of Chicago*

HORMONES AND THEIR INFLUENCE ON THE EMOTIONS

FRANCIS J. BRACELAND, *Psychiatrist-in-Chief, Institute of Living; Clinical Professor of Psychiatry, Yale University*

MORNING PANEL PROGRAM

Wednesday, October 8

PRACTICAL CONSIDERATIONS REGARDING REALISM AND WISHFUL THINKING IN ENDOCRINE THERAPY

Chairman: RUSTIN MCINTOSH

Friday, October 10

PRACTICAL CONSIDERATIONS REGARDING THE USE OF ACTH AND CORTISONE

Chairman: LOUIS LEITER

Wednesday, October 15

PRACTICAL CONSIDERATIONS REGARDING DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN DISORDERS OF THE THYROID GLAND

Chairman: DAVID P. BARR

Friday, October 17

PRACTICAL CONSIDERATIONS REGARDING HORMONAL MANAGEMENT OF MALIGNANT NEOPLASMS

Chairman: C. P. RHOADS

HOSPITAL CLINICS PROGRAM

All Clinics will be held from 2 to 5 P.M.

CALENDAR OF CLINICS

First Week

Monday, October 6	1.	Bellevue *Hospital Representative*: CHARLES F. WILKINSON, JR.
	2.	Montefiore *Hospital Representative*: SAMUEL M. SEIDLIN
Tuesday, October 7	3.	New York *Hospital Representative*: EPHRAIM SHORR
	4.	Flower-Fifth Avenue *Hospital Representative*: CLAIR E. FOLSOME
Wednesday, October 8	5.	University *Hospital Representative*: LOCKE L. MACKENZIE
	6.	Veterans Administration *Hospital Representative*: BERNARD STRAUS
Thursday, October 9	7.	Presbyterian *Hospital Representative*: JOSEPH W. JAILER
	8.	Morrisania *Hospital Representative*: EDWARD P. FLOOD
Friday, October 10	9.	Mount Sinai *Hospital Representative*: LOUIS J. SOFFER
	10.	Bellevue *Hospital Representative*: CHARLES F. WILKINSON, JR.

Second Week

Monday, October 13	11.	Mount Sinai *Hospital Representative*: SOLOMON SILVER
	12.	Beth Israel *Hospital Representative*: ARTHUR M. FISHBERG
Tuesday, October 14	13.	New York *Hospital Representative*: EPHRAIM SHORR
	14.	Montefiore *Hospital Representative*: SAMUEL M. SEIDLIN
Wednesday, October 15	15.	Roosevelt *Hospital Representative*: JOHN E. HUTTON
	16.	Polyclinic *Hospital Representative*: JAMES P. CROCE
Thursday, October 16	17.	Presbyterian *Hospital Representative*: JOSEPH W. JAILER
	18.	St. Luke's *Hospital Representative*: WILLIAM NORTON, II
Friday, October 17	19.	Harlem *Hospital Representative*: ALEXANDER ALTSCHUL
	20.	Memorial *Hospital Representative*: RULON W. RAWSON

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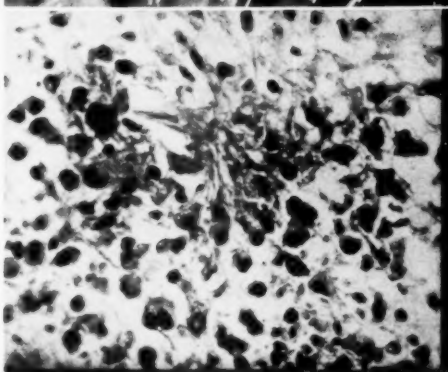
1. Behrman, H. T., Combes, F. C., Bobroff, A., Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
2. Turell, R.: New York St. J.M. 50:2282, 1950.
3. Heimer, C. B., Grayzel, H. G., and Kramer B.: Archives Pediat. 68:382, 1951.

response in rheumatic fever

q. Does cortisone influence the heart lesions of rheumatic fever?

a. Early cortisone administration suppresses and in some cases may even prevent serious cardiac damage.



q. What effect does cortisone have on acute rheumatic fever?

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*Brown et al.: Ann. Allergy, 8:32, 1950.

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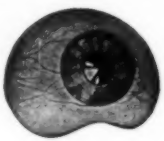

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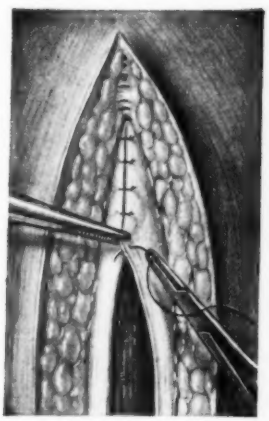

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1. *Seley, S. A.: Am. J. Dig. Dis. 13:238 (July) 1946.* 2. *Rossien, A. X.: Rev. of Gastroenterol. 16:34-52 (Jan.) 1949.* 3. *Rossien, A. X. and Victor, A. W.: Am. J. Dig. Dis. 14:226-229 (July) 1947.* 4. *Batterman, R. C. and Ehrenfeld, I.: Gastroenterol. 9:151 (August) 1947.*

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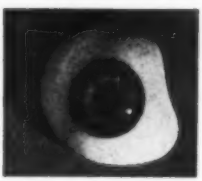

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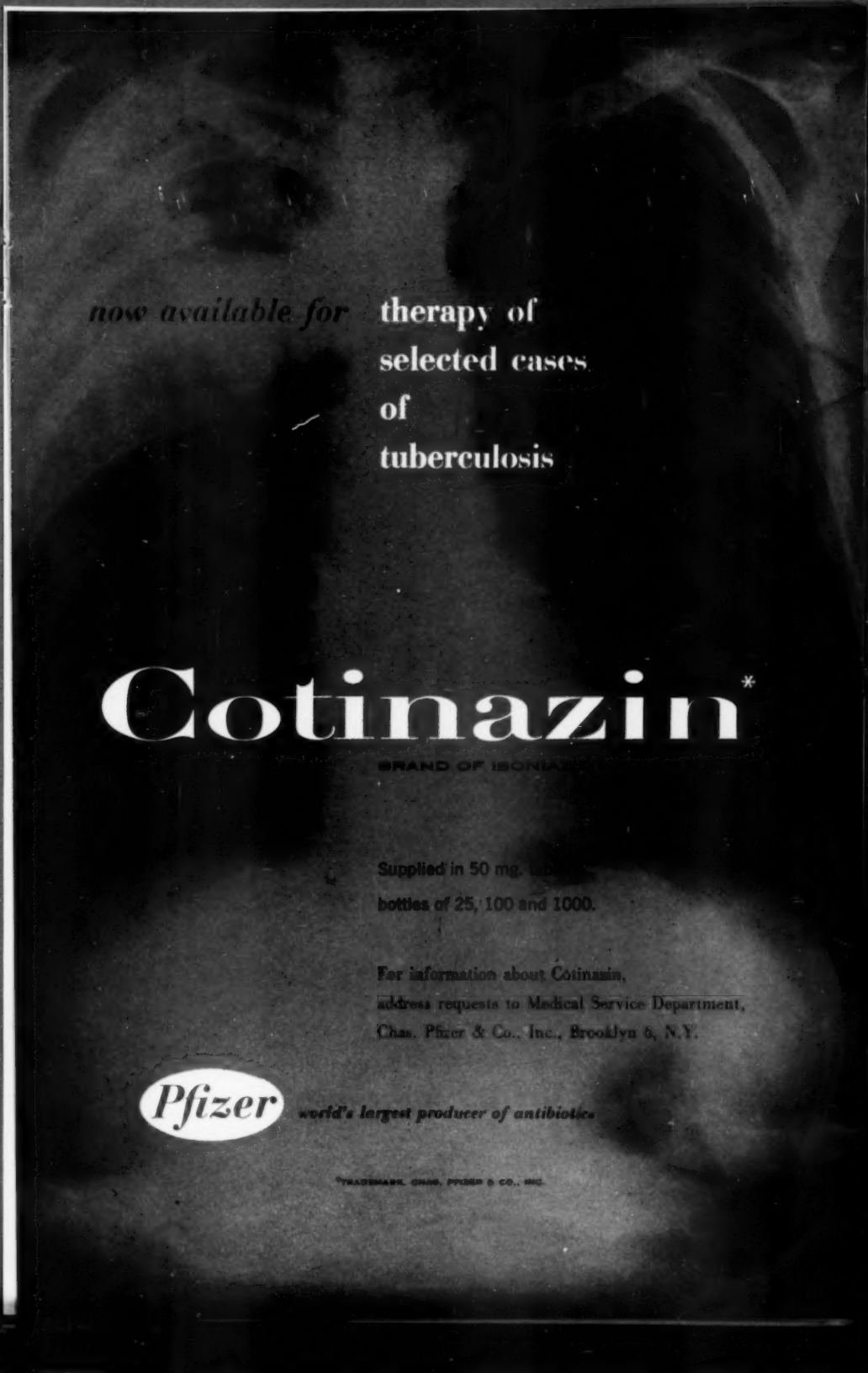
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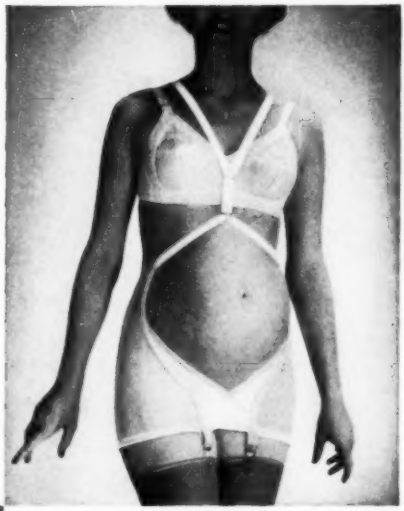

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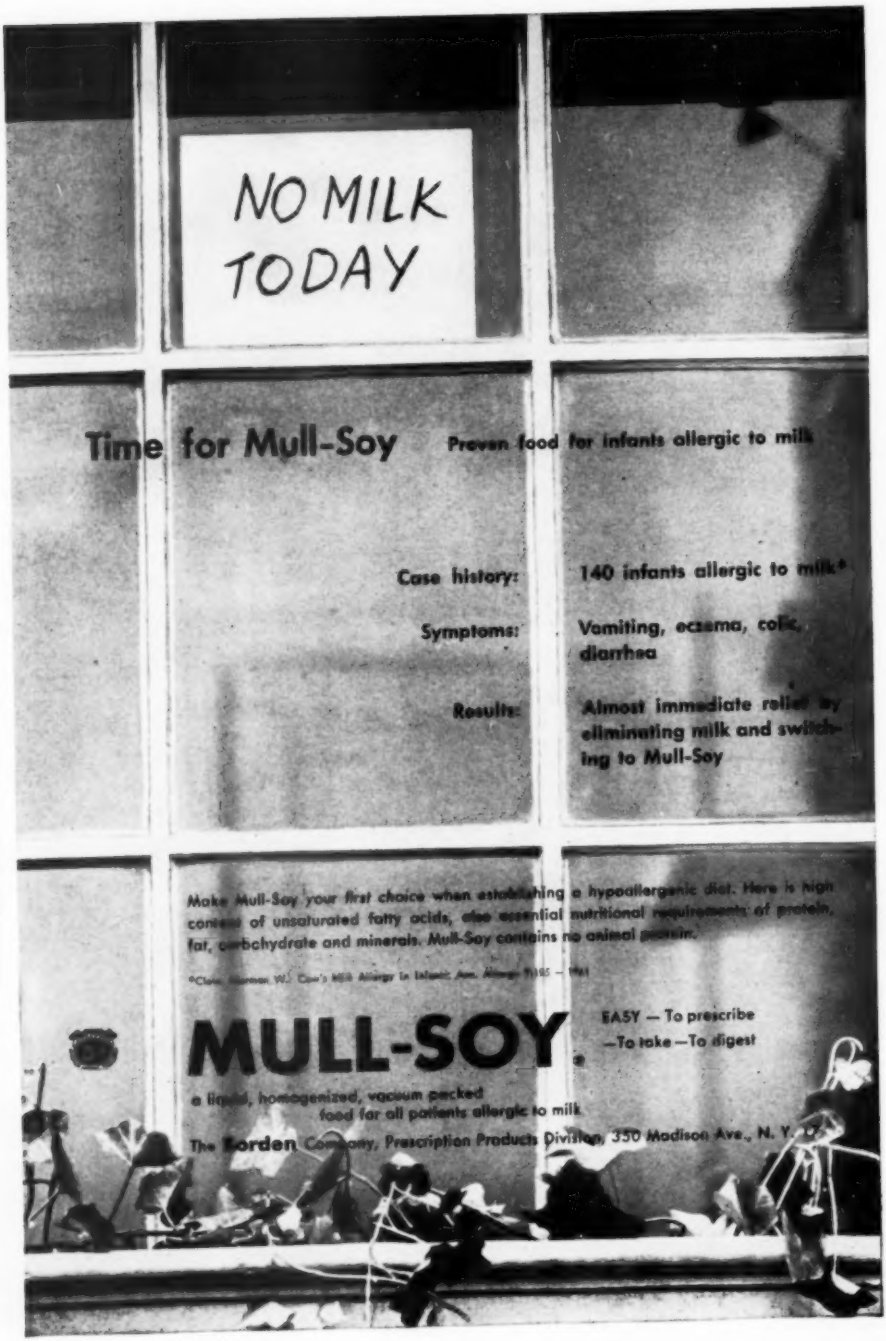
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*Talkov, R. H., Ropes, M. W., and Bauer, W.: *The Value of Enteric Coated Aspirin.* N.E.J. Med. 242.19 (Jan. 5) 1950.

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